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1. Ranucci M, Aloisio T, Carboni G, et al. Acute Kidney Injury and Hemodilution During Cardiopulmonary Bypass: A Changing Scenario. *Ann Thorac Surg.* 2015;100:95-100.

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Perfusion

What is going on?

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If there ever was a provocative title for an editorial, this one would qualify. The message herein does not refer to the political scene, 5G technology, or the odds of an asteroid hitting planet earth this year. Instead, the focus is on the journal—what happened in 2020 and what we can anticipate for 2021.

First, in the year just past: manuscript submissions to *Perfusion* were up by approximately 33% over the previous year and exceeded 400 in 2020. Not all this increase was due to reports on the pandemic crisis, but, like many medical journals in recent months, there were many submissions reporting how clinicians have been dealing with the overwhelming number of infected patients. In fact, papers in *Perfusion* with "COVID" or "pandemic" in the title, beginning with an editorial[1] in the May issue, accounted for nearly 10% overall in the latter half of 2020 and included additional editorials[2–4] and several original papers, cases reports, and Letters to the Editor. This trend will no doubt continue this year as the number of cases and hospitalized patients needing urgent healthcare because of the virus will continue to rise.

Second, as you may have noticed by the number of original papers published in recent issues, the publisher has increased the page count per issue (to 108 from 88) in response to this surge in submissions and overall "health" of the journal in readership and advertising. As has been the case the last 3 years, there are nine issues planned for 2021 including a Supplement.

Another major positive development has been completion of a formal affiliation agreement between the publisher and EuroELSO, whereby *Perfusion* is now designated as their official journal. In that regard, you will note the addition of Dr Jan Bělohlávek as an Associate Editor. He is based at Charles University of Prague, where he is an Associate Professor of Medicine and Consultant in Cardiology and Critical Care. In these roles, he oversees the Cardiac Intensive Care Unit and coordinates their busy ECMO team. Dr Bělohlávek is widely published, the current president of EuroELSO, and former program chair for their congress held in 2018. Jan has been an invaluable reviewer and advocate in strengthening journal ties to the EuroELSO community over the last few years. Also, and in further recognition of this affiliation, four active EuroELSO clinicians will be named to the Advisory Editorial Board and tasked with editorial duties for EuroELSO submissions. In recent years, the journal has published EuroELSO abstracts for their annual conference, in print or online, in a Supplement along with selected, peer-reviewed manuscripts from its members. This initiative is to continue and will grow in 2021.

Additionally, and as a testament to the international scope of the journal, submissions and published manuscripts from China have increased thanks in large part to the influence and efforts of Dr Xiatong Hou, another Associate Editor who was appointed in this role in 2019. Dr Hou is based at Beijing Anzhen Hospital, Capital Medical University, which is China's most active medical center. They see 2.6 million patients every year and perform an astounding 10,000 cardiac surgery cases annually including heart, lung, and heart and lung transplantation. In addition, they, too, have an active ECMO program for patients of all ages. Dr Hou is an attending cardiac surgeon, Chief of the Cardiac Intensive Care (>100 beds!), and Director of Extracorporeal Circulation at his facility.

I wish to pay tribute to Dr Geoffrey Lockwood, Consultant Anesthetist at the Hammersmith Hospital in London, who is retiring after serving as an Associate Editor for the journal after 6 years. Geoff has worked in the cardiac operating room with Editor-in-Chief, Mr Prakash P Punjabi, for over two decades, and we shall miss his insightful editorials and carefully crafted critiques of manuscripts during the peer review process. He always brings a unique perspective as a reviewer and editor.

Other news recently disclosed by SAGE Publishers is that the geographic distribution of visitors to journal content via Google Scholar or the US National Institutes of Health portals generally mirror manuscript submissions from around the world dominated by China, United States, Taiwan, the UK, and Turkey.

Another new journal initiative in 2021 will be the availability of a digital edition of this issue of *Perfusion* for members and meeting delegates to the American Academy of Cardiovascular Perfusion's (AACP) annual

seminar. A digital edition is a convenient cover-to-cover flipbook in PDF format that will increase exposure of *Perfusion* beyond the print edition by expanding electronic dissemination of its content. This initiative is being kindly sponsored by Medtronic USA. The strong affiliation between the journal and the AACP began in the 1990s and has provided a scholarly outlet for AACP peer-reviewed manuscripts to be published and disseminated internationally.

Finally, the current issue: you will note the wide variety of content including invited commentary, reviews, original studies, practical techniques, case reports, and Letters to the Editor. This has characterized the journal since its inception in 1986 under the guidance of Editor Emeritus, Professor Ken Taylor, to whom we are indebted for always being a strong proponent for all aspects of the science of extracorporeal circulation and related technologies.

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References

1. Toomasian J. Editorial. The COVID-19 pand-ECMO-ic. *Perfusion* 2020; 35: 278–279.
2. Punjabi PP. Editorial. COVID-19: ethnic, cardiovascular and renal: pandemic causing pandemonium. *Perfusion* 2020; 35: 451.
3. Toomasian JM. Editorial. The COVID summer of 2020. *Perfusion* 2020; 35: 572–573.
4. Punjabi PP. Editorial. The second coming—deluge, surge, vaccinate, wane, dwindle, overcome. *Perfusion* 2020; 35: 716.

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Commentary on "Outcomes of out-of-hospital extracorporeal membrane oxygenation transfers: significance of initiation site and personnel"

W Cory Ellis

The use of a "hub and spoke" model for providing ECMO support is increasingly common among health systems. The hub and spoke model allows critically ill patients to be placed on ECMO support at any of the health system centers (the spoke) and once stabilized patients are transferred to a specific ECMO designated center (the hub) for management during the ECMO support period. This model allows for a concentrated experience in management while still maintaining the ability to provide ECMO support when necessary at outlying centers. The article titled "Outcomes of out of hospital transfers: significance of initiation site and personnel," by Mihama et al. describes challenges and successes relative to the use of this model at their center.[1] The aim of this commentary is to point out the non-conventional use of some terminology within the manuscript. The terminology is defined within the manuscript itself, however, it is important for readers to note that the terms "ECMO specialist, low volume ECMO center and non-ECMO center," as used within the manuscript are not aligned with traditional usage of those terms and may be confusing.

In the manuscript the authors use the terms low volume and non-ECMO center interchangeably. Low volume ECMO centers support fewer than 6 ECMO patients annually and have significantly increased mortality according to Barbaro et al.[2] The Extracorporeal Life Support Organization (ELSO) recommends that the "cost effectiveness of providing fewer than 6 cases per year combined with the loss, or lack of clinical expertise associated with treating fewer than this number of patients per year should be taken into account when developing a new program."[3] It should be noted, however, that there are ECMO centers around the world who provide support for fewer than six patients. These centers, while low volume, have a programmatic structure in place that falls in line with ELSO guidelines and include: A program director who oversees the entire program, an ECMO coordinator who supervises and oversees the technical staff, a robust quality assurance program for ECMO supported patients and formal policies and procedures guiding clinical management and program maintenance.[3] Non-ECMO centers do not have a formalized structure in place to initiate ECMO support and subsequently manage ECMO patients in their center. In the hub and spoke model, outlying, non-ECMO, centers (the spokes) may have the technical skills necessary to initiate ECMO support with a plan to transfer patients to a single ECMO center within the health system (the hub) where a formalized structure provides more concentrated experience. The interchangeable use of the terms low volume and non-ECMO center may be confusing to readers.

Commonly the term ECMO specialist, or ECMO clinical specialist, describes the person responsible for the day to day management of the ECMO circuit and program. ELSO guidelines define the ECMO specialist as "the technical specialist trained to manage the ECMO system and the clinical needs of the patient on ECMO under the direction and supervision of a licensed ECMO trained physician."[4] ECMO specialist, as defined by ELSO, may be physicians, nurses, respiratory therapists, perfusionists or biomedical engineers,[2] however, around the world ECMO specialist teams are most commonly a group of ECMO trained ICU nurses who remain at the bedside of ECMO supported patients throughout the entire ECMO run under the direction of ECMO trained

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physicians who may have responsibility for managing all patients in an ICU during their service period. In the manuscript the authors use the term ECMO specialist to describe all team members trained in ECMO management and include surgeons, ICU physicians, perfusionists and nurses with specific ECMO training under the umbrella term "ECMO specialist." This usage should be noted by readers to avoid confusion where the term ECMO specialist commonly refers to a specific role within ECMO programs.

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References

1. Mihama T, Liem S, Cavarocchi N, et al. Outcomes of out-of-hospital extracorporeal membrane oxygenation transfers: significance of initiation site and personnel. *Perfusion* 2020; 35: 633–640.
2. Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med* 2015; 191: 894–901.
3. Extracorporeal Life support Organization. ELSO guidelines for ECMO centers v1.8, https://www.elso.org/Portals/0/IGD/Archive/FileManager/faf3f6a3c7cusersshyerdocumentselsoguidelinesecmocentersv1.8.pdf (2014, accessed 3 January 2020).
4. Extracorporeal Life support Organization. ELSO guidelines for training and continuing education of ECMO specialists, https://www.elso.org/Portals/0/IGD/Archive/FileManager/97000963d6cusersshyerdocumentselsoguidelinesfortrainingandcontinuingeducationofecmospecialists.pdf (2014, accessed 3 January 2020).

Review

Perfusion

Minimally invasive cardiac valve surgery during the COVID-19 pandemic: to do or not to do, that is the question

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Daniel Paul Fudulu, Gianni D Angelini and Hunaid A Vohra

Overview

Minimally invasive cardiac surgery (MICS) is now an established technique in many centres across Europe and the USA. Studies, mostly observational, have shown potential benefits in terms of increased patient satisfaction, reduced wound infections, improved postoperative respiratory function, faster recovery, reduced blood transfusions and improved cost-effectiveness with MICS when compared to conventional approaches.[1–3] However, recently published randomised trials comparing mini-sternotomy aortic valve replacement (AVR) with conventional AVR have shown no clear benefit.[4–6] Randomised data looking at the potential benefits of mini-thoracotomy AVR are still awaited; however, some observational studies have shown that this holds a promise.[7,8] When it comes to minimally invasive mitral valve repair, the results of a critical randomised controlled trial are still awaited.[9] Nevertheless, there is a general agreement in the literature, that hard end-points such as short- and long-term survival after MICS are the same with the two techniques. From our experience, MICS remains a highly desirable choice for our patients and cardiology colleagues that are in the search for less invasive strategies.

Like any other surgical speciality, the COVID-19 pandemic has also profoundly affected cardiac surgical practice with activity halted transiently in order to maximise the availability of intensive care beds, ventilators and staff for patients affected by acute respiratory distress.[10] At present, cardiac services are gradually aiming to return to the pre-COVID state, as there is a steady decline in the number of new cases and COVID-related deaths leading to increased relaxation of social distancing.[11] However, this could be severely hampered if a second COVID peak occurs, which would further delay treatment and significantly contribute to valve-related mortality of patients on the MICS waiting list.

During these unprecedented times, due to factors related to staff, experience, equipment and potential infection, we herein reflect if we should be doing MICS.

Preoperative planning

Firstly we should bear in mind that patients may have already consented in advance to undergo MICS. Unless a strong anatomical or a new clinical reason to abandon MICS is deemed appropriate in the interest of patient safety, last-minute changes in consent are not good practice and lead to patient disappointment/complaints, loss of patient choice and reputation of the minimally invasive cardiac surgical service.

Careful triage of patients should be undertaken whilst contemplating MICS during COVID-19 pandemic. In our view, all frail patients and octogenarians should be postponed. The prohibitively high mortality risk of COVID-19 positive patients undergoing surgery in general[12] coupled with the significant COVID-19 related mortality in octogenarians[13] outweighs the risk of delaying the cardiac procedure. Patients with critical cardiac pathology should have an intervention. For example, patients with aortic valve area of $\leqslant 0.5\,cm^2$ and peak gradient >100 mmHg across the aortic valve or very severe mitral insufficiency with worsening symptoms meet such criteria such frail patients with critical conditions should be better served with TAVI, particularly in this period.

There is no doubt that emergency surgery during the COVID-19 pandemic should be done by conventional approach whatever the COVID-19 swab result might be.

Established referral pathways and theatre protocols that aim to reduce the risk of COVID-19 spread from patient to staff or vice-versa are now universally implemented.[14] It is mandatory for patients listed for cardiac surgery to have nasopharyngeal swabs tested negative for COVID-19 and all elective patients to

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have completed 2 weeks of self-isolation.[15] Despite such rigorous screening, the potential risk of patients undergoing planned MICS acquiring COVID-19 during their hospital stay is likely to be the same as conventional surgery. This risk is not negligible and is the range of 5% to 20%.[14]

While computer tomography (CT) chest was being routinely performed at the beginning of the pandemic in asymptomatic patients listed for conventional elective cardiac surgery to exclude COVID-19 related pneumonitis, this approach has now been abandoned due to lack of evidence.[16] However, in the case of MICS, many centres perform CT chest anyways to plan the minimal access approach. If available, a recent CT chest can further inform the surgeon on the presence or absence of COVID-19 pneumonitis, and it should not be overlooked.

Intraoperative aspects

COVID-19 virus can be transmitted in the operating theatre via aerosolisation. Manoeuvres such as intubation of the trachea, a breach in the lung during the procedure and possibly with the use of an electric saw during sternotomy harbour this risk. One could argue that MICS, by avoiding a sternotomy, reduces aerosolisation; however, by employing mini-thoracotomy, MICS may be associated with a higher risk of lung injury as compared to a midline sternotomy. The application of robotically-assisted MICS, in theory, could reduce the transmission of COVID-19 to both patient and staff as a considerable part of the operation is performed through a remote console.[17]

In the current climate, the use of specialised personal protective equipment (PPE) in the theatre environment is paramount as all patients undergoing surgery should be treated as potentially COVID-19 infected, despite a negative swab. This is justified by the considerable high false-negative rate of the RT-PCR tests of up to 29%.[18] This leads to a high-pressure environment where an attempt is made to minimise personnel in theatre. The use of FFP-3 masks during prolonged operations can cause discomfort. Moreover, the adoption of motor-powered hoods in confined theatre spaces creates noise, affects communication and threatens sterility. While attempting to adhere to these tight precautions, there is a tendency to expose the team to more significant fatigue and lack of concentration which could be associated with poor outcomes. MICS requires a dedicated team and is generally associated with longer cross-clamp times and cardiopulmonary bypass times compared to conventional procedures. The factors mentioned above, especially in inexperienced hands, may result in prolonged exposure of the theatre staff and patient to potential infection, exposure to stress and inappropriate delays. In case a situation arises where conversion to a sternotomy is required during MICS, timely, agile coordination between the personnel both inside and outside operating room will be vital for a good patient outcome. Hence, a dedicated, experienced team in MICS should be allocated to all such cases, especially so in a pandemic situation. During such unprecedented times, surgery should be performed in referral centres with an established programme in MICS. Any training should be postponed till return to a normal clinical activity.

Postoperative considerations

The potential quicker reported recovery and earlier discharge of patients after MICS minimises the exposure of patients to the risk of acquiring nosocomial COVID-19 and can lead to improved patient flow at a time of high demand for hospital beds. Therefore, high-risk patients who have undergone MICS would potentially derive this additional benefit of early recovery, which we have reported in the past.[19]

We could only hypothesise, that the preservation of immunity observed after minimally invasive surgery compared to conventional surgery could provide additional benefits.[20] It unclear if this ultimately translates into better clinical outcomes. However, it would be fascinating to know the comparison of outcomes during the pandemic with MICS versus conventional surgery. Such subgroup analyses will likely be available in the future.

Conclusion

In experienced centres, MICS should continue the be practised during the COVID-19 pandemic but with careful selection of elective patients. Octogenarians should be postponed while emergency cases should be done via conventional approach. Setting up of a new MICS programme should be deferred until the pandemic is over and implementation is done based on principles of clinical governance.[21] Results of MICS from national and international databases during the COVID-19 pandemic are eagerly awaited.

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References

1. Fudulu D, Lewis H, Benedetto U, et al. Minimally invasive aortic valve replacement in high risk patient groups. *J Thorac Dis*. 2017; 9: 1672.
2. Phan K, Xie A, Di Eusanio M, et al. A meta-analysis of minimally invasive versus conventional sternotomy for aortic valve replacement. *Ann Thorac Surg*. 2014; 98: 1499–1511.
3. Schmitto JD, Mokashi SA, Cohn LH. Minimally-invasive valve surgery. *J Am Coll Cardiol*. 2010; 56: 455–462.
4. Hancock HC, Maier RH, Kasim AS, et al. Mini-sternotomy versus conventional sternotomy for aortic valve replacement. *J Am Coll Cardiol*. 2019; 73: 2491–2492.
5. Nair SK, Sudarshan CD, Thorpe BS, et al. Mini-stern trial: a randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement. *J Thorac Cardiovasc Surg*. 2018; 156: 2124–2132.e31.
6. Kirmani BH, Jones SG, Malaisrie SC, et al. Limited versus full sternotomy for aortic valve replacement (review) summary of findings for the main comparison. *Cochrane Database Syst Rev*. 2017; 4: CD011793, https://www.ncbi.nlm.nih.gov/pubmed/28394022%0Ahttp://doi.wiley.com/10.1002/14651858.CD011793.pub2
7. Glauber M, Miceli A, Gilmanov D, et al. Right anterior minithoracotomy versus conventional aortic valve replacement: a propensity score matched study. *J Thorac Cardiovasc Surg*. 2013; 145: 1222–1226, https://www.jtcvs.org/article/S0022522312004205/fulltext (accessed 24 June 2020).
8. Del Giglio M, Mikus E, Nerla R, et al. Right anterior mini-thoracotomy vs. conventional sternotomy for aortic valve replacement: a propensity-matched comparison. *J Thorac Dis*. 2018; 10: 1588–1595, https://pmc/articles/PMC5906311/?report=abstract (accessed 24 June 2020).
9. Uk Mini Mitral Trial, https://ukminimitral.co.uk/ (accessed 16 June 2020).
10. Fudulu DP, Angelini GD. Cardiac surgery in the time of the coronavirus. *J Card Surg*. 2020; 35: 1177–1179, https://onlinelibrary.wiley.com/doi/abs/10.1111/jocs.14580 (accessed 9 June 2020).
11. Coronavirus (COVID-19) in the UK, https://coronavirus.data.gov.uk/#category=nations&map=rate (accessed 18 June 2020).
12. Archer JE, Odeh A, Ereidge S, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020, https://www.thelancet.com/article/S014067362031182X/fulltext (accessed 24 June 2020).
13. Coronavirus (COVID-19) roundup - Office for National Statistics, https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19roundup/2020-03-26 (accessed 16 June 2020).
14. SCTS/ACTACC/SCPS Theatre COVID pathway, 2020, https://scts.org/wp-content/uploads/2020/03/SCTS-ACTACC-SCPS-Theatre-COVID-pathway-Final.pdf (accessed 18 May 2020).
15. NHS England » NHS roadmap to safely bring back routine operations, https://www.england.nhs.uk/2020/05/nhs-roadmap/ (accessed 16 June 2020).
16. Current recommendations regarding preoperative COVID-19 screening CT scan in patients undergoing cardiothoracic surgery, 2020, https://scts.org/covid-19/ (accessed 18 May 2020).
17. Van den Eynde J, De Groote S, Van Lerberghe R, et al. Cardiothoracic robotic assisted surgery in times of COVID-19. *J Robot Surg*. 2020; 1–3.
18. Watson J, Whiting PF, Brush JE. Interpreting a covid-19 test result. *BMJ*. 2020; 369. https://www.bmj.com/content/369/bmj.m1808
19. Rayner TA, Fudulu D, Nashef S. A career in cardiothoracic surgery. *BMJ*. 2019; 367: l5914.
20. Walker WS, Leaver HA. Immunologic and stress responses following video-assisted thoracic surgery and open pulmonary lobectomy in early stage lung cancer. *Thorac Surg Clin*. 2007; 17: 241–249.
21. BISMICS & SCTS Statement on Minimally Invasive Surgery. May 2020: 1–2. https://scts.org/covid-19/ (accessed 18 May 2020).

Review

Perfusion

Clinical outcomes associated with retrograde arterial perfusion in minimally invasive mitral valve surgery: a systematic review

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Abstract

Introduction: Given several reports of an increased neurologic risk with retrograde arterial perfusion in minimally invasive mitral valve surgery, we sought to identify and synthesize the best available evidence on the influence of perfusion strategy on post-operative clinical outcomes in this population.

Methods: A systematic search of PubMed, EMBASE, MEDLINE, and Cochrane library databases was performed to identify publications comparing clinical outcomes associated with antegrade and retrograde arterial perfusion in minimally invasive mitral valve surgery. Pre-specified outcomes of interest were neurologic events, mortality, and renal failure. The search was performed by two independent reviewers, with data abstraction following.

Results: Seven observational studies were included in this review, with a total patient population of 5,385. Six were retrospective cohort in design, with a single small prospective cohort study identified. When available, adjusted publication-specific risk estimates were abstracted and included preferentially over unadjusted or reviewer-derived risk estimates. Meta-analysis was felt to be heavily flawed in the context of few small studies identified and was not performed. In adjusted estimates, there appeared to be an increased risk of neurologic complications with retrograde arterial perfusion. There was a null pattern apparent between arterial perfusion strategy and each of 30-day mortality and renal failure.

Conclusion: Retrograde arterial perfusion in minimally invasive mitral valve surgery may be associated with an increased risk of neurologic events, without affecting the risk of 30-day mortality or renal failure. Although these patterns were identified, an overall paucity of evidence justifies further study.

Keywords

minimally invasive; mitral valve; perfusion strategy; review; clinical outcomes

Introduction

As the frequency of minimally invasive mitral valve surgery (MIMVS) increases, concerns have been raised with respect to the perfusion strategy and the patient's clinical risk profile. Although certain centers have moved toward central cannulation and antegrade arterial perfusion, the typical setup for minimally invasive mitral surgery still employs retrograde arterial perfusion via the patient's femoral artery.[1,2] An increased risk of neurologic events is a common concern in this patient population, although evidence is inconsistent and overwhelmingly from observational studies.[3]

In the current era, mitral valve repair procedures are recommended to select asymptomatic patients with preserved left ventricular function.[4] Minimally invasive procedures are an increasingly popular option for patients, and adequate understanding of the risk profile of the procedure setup is crucial. Given these concerns for the risk of adverse clinical outcomes, we performed a systematic review of the best available comparative evidence for patients undergoing MIMVS via a right thoracotomy. Our goal was to evaluate the association between an antegrade or retrograde perfusion strategy and the risk of neurologic complications, mortality, and renal failure.

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Materials and methods

Record identification and data extraction

A systematic search strategy was developed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[5] MEDLINE, EMBASE, PubMed, and the Cochrane Library were each searched using specific text terms and the same constructed search string. The following terms were included:

1. Mitral;
2. Mitral valve;
3. Mitral valve repair;
4. Minimally invasive;
5. Minimally-invasive;
6. Keyhole;
7. Port access;
8. Central;
9. Aortic;
10. Direct aortic;
11. Femoral;
12. Femoral artery;
13. Cannulation.

The search string constructed was as follows:

(1 OR 2 OR 3) AND (4 OR 5 OR 6 OR 7) AND
(8 OR 9 OR 10 OR 11 OR 12) AND 13

Our patient population included adult patients undergoing right thoracotomy–based MIMVS. Retrograde femoral arterial perfusion was considered the exposure of interest, compared with antegrade direct aortic perfusion. The incidence of neurologic complications was prespecified as the primary outcome of interest. Secondary outcomes included mortality and renal failure. To be included, articles were required to meet the following selection criteria:

1. Comparative studies of cannulation strategy in minimally invasive mitral surgery via right thoracotomy;
2. Included evaluation of one or more of the specified outcomes of interest (neurologic events, mortality, renal failure);
3. Minimally invasive mitral surgery standing as the primary operation;
4. An existing systematic review/meta-analysis studying minimally invasive mitral surgery;
5. Full-text available, not unpublished "gray literature";
6. Published in English.

Included systematic reviews/meta-analyses were surveyed for relevant citations. These citations would undergo a full-text evaluation and would be included if the above criteria were met. Published studies were excluded if they were non-comparative studies (such as case reports or series), basic science, "how to" articles, or gray literature (published abstracts without accompanying full-text publications). Publications without a specific MIMVS population were excluded, as were those studies that did not compare perfusion strategies. Finally, in order to keep study populations as similar as possible, publications comparing sternotomy-based approaches to thoracotomy-based mitral surgery were excluded.

The records obtained from the literature search were independently reviewed and screened by two co-authors (D.J.P.B. and R.B.), with controversy between publications resolved by mutual discussion. This was followed by data extraction for each individual publication, focusing on study demographics, outcomes reported, outcome definitions, population/intervention group inclusion criteria, recruitment methods, and statistical adjustment methods. During data extraction, each of the previously mentioned co-authors reviewed each included full-text publication and tabulated relevant information independently to ensure completeness. Quality assessment of identified observational studies was performed in accordance with the Newcastle–Ottawa scale for quality assessment of non-randomized studies.[6]

Statistical analysis

Each included publication was examined for reported comparative statistics for the outcomes of interest. When available, adjusted risk estimates have been reported preferentially over unadjusted or univariable results. If no comparative statistic was reported, then the unadjusted odds ratio (OR) and accompanying 95% confidence interval (CI) were calculated using the binary event rates reported by the study publication. Event incidences were reported in line with the OR. When faced with "zero-event" occurrences, only the event incidences have been reported. All statistical analysis was carried out using Stata 13.1 (StataCorp LP, College Station, TX, USA). CIs were set at 95%; all p values were two-sided and considered statistically significant if <0.05. Where possible, exact p values have been reported.

Results

Publication selection and characteristics

After the removal of duplicate records, 248 records were screened for inclusion by title and abstract. Following

this, 21 records were selected for full-text review. After full-text review, eight publications were selected for inclusion. One potentially relevant full-text publication was inaccessible; this was a small study of 20 patients.[7] The single included systematic review did not yield any additional publications.[3] In total, seven publications were included for review and analysis, providing a pooled total of 5,385 patients. Full details of the systematic search strategy are reported in Figure 1. All included studies were observational; no randomized studies were included. Six publications were of retrospective cohort design, with a single included prospective cohort study identified.

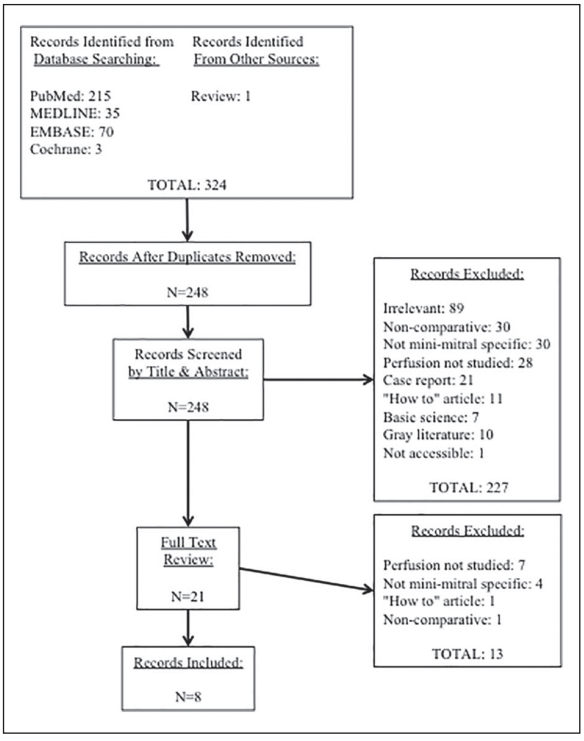

Figure 1. Search strategy results, adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Included studies were published between 1998 and 2017, with six being published from 2010 onward. Patient populations varied widely, with the smallest population being 106 and the largest being 1,632. Only two countries were represented, with four publications originating from Italy (two of these were from the same Italian group).[8–11] The three remaining publications originated from the United States.[1,12,13] Not every outcome of interest was reported in every publication, and outcome definitions varied between publications as well. Publication-level demographics, including outcomes reported, are reported in Table 1. Formal outcome definitions were largely lacking, with methods of validating said outcomes typically not defined (Table 2).

Important methodological heterogeneity existed between publications (Table 3). Enrollment procedures varied between publications, with only two publications reporting criteria for undergoing MIMVS.[9,12] For perfusion strategy allocation, two publications ultimately relied on the discretion of the operating surgeon, with only one reporting a protocol for assessing the most appropriate perfusion strategy.[8–10] Four publications left allocation strategy unspecified. Aortic occlusion strategies included both endoaortic balloon occlusion and transthoracic clamping, with three publications including both techniques.[1,9,10] Concomitant procedures included those commonly associated with mitral procedures. One publication reported a single patient who underwent concomitant coronary artery bypass grafting via the same right thoracotomy approach.[11] Patient and operative characteristics varied by publication, and often between groups (Table 4). Not every publication reported these characteristics by perfusion group. When reported, the retrograde group tended to be younger. The retrograde group also tended to have longer cardiopulmonary bypass and cross-clamp times. Predictably, where imaging studies of the patient's vasculature were obtained to drive the perfusion strategy decision, the retrograde group had a far lower prevalence of peripheral vascular disease.[9] The other characteristics failed to show a consistent trend

Table 1. Publication characteristics.

Publication	Design	Study dates	Region	Population			Outcomes reported		
				AAP	RAP	Total	Neurologic	Mortality	Renal
Murzi et al.[8]	RC	2003-2015	Italy	1,491	141	1,632	✓	✓	✓
Barbero et al.[9]	RC	2009-2014	Italy	63	397	460	✓	✓	✓
Bedeir et al.[12]	RC	2004-2012	USA	327	57	384	✓	✓	✓
Murzi et al.[10]	RC	2003-2012	Italy	1,113	167	1,280	✓	✓	✓
Grossi et al.[1]	RC	1995-2007	USA	888	394	1,282	✓	–	–
Ricci et al.[11]	RC	1997-2007	Italy	112	129	241	✓	–	–
Aklog et al.[13]	PC	1996-1998	USA	87	19	106	–	✓	–

RC: retrospective cohort; PC: prospective cohort; AAP: antegrade arterial perfusion; RAP: retrograde arterial perfusion.

Table 2. Outcome definitions and validation methods by publication.

Publication	Neurologic		Mortality		Renal Failure	
	Definition	Validation	Definition	Validation	Definition	Method
Murzi et al.[8]	New focal neurologic deficit	Daily care physician, imaging, neurologist	30 days	ND	Acute kidney injury	New HD or SCr >200 μmol/L
Barbero et al.[9]	ND	ND	30 days	ND	Acute kidney injury	New HD
Bedeir et al.[12]	ND	ND	30 days	ND	ND	ND
Murzi et al.[10]	New focal neurologic deficit	Daily care physician, imaging, neurologist	30 days	ND	Acute kidney injury	New HD or SCr >200 μmol/L
Grossi et al.[1]	New permanent deficit, transient deficit greater than 24 hours, or new lesion on cerebral imaging	ND	NR	–	NR	–
Ricci et al.[11]	ND	ND	NR	–	NR	–
Aklog et al.[13]	NR	NR	Operative	ND	NR	–

ND: not defined; NR: not reported; HD: hemodialysis; SCr: serum creatinine.

Table 3. Publication methodology.

Publication	Criteria for MIMVS	Perfusion group allocation	Aortic occlusion	Concomitant procedures	Adjustment methods
Murzi et al.[8]	NS	Risk profile and surgeon's discretion	Temporal shift: endoballoon to transthoracic clamp	Tricuspid repair, ablation	Multivariable regression
Barbero et al.[9]	Absence of ⩾ moderate AI, severe lung adhesions, hostile chest for a minimally invasive approach, hemodynamic instability	Imaging screen determined	Endoballoon and transthoracic clamp	Tricuspid repair, ASD/PFO closure, ablation	Multivariable regression[a]
Bedeir et al.[12]	Isolated MIMVS, >60 years using transthoracic clamping with the absence of preoperative shock or endocarditis	NS	Transthoracic clamp	None	Multivariable regression
Murzi et al.[10]	NS	Surgeon's discretion	Temporal shift: endoballoon to transthoracic clamp	Tricuspid repair, ablation	Multivariable regression and propensity scoring
Grossi et al.[1]	NS	NS	Endoballoon and transthoracic clamp	None	Multivariable regression
Ricci et al.[11]	NS	NS	Endoballoon	Tricuspid repair, ASD/PFO closure, CABG (1 case)	None
Aklog et al.[13]	NS	NS	Transthoracic clamp	Tricuspid repair, ASD/PFO closure	None

MIMVS: minimally invasive mitral valve surgery; NS: not specified; ASD: atrioseptal defect; PFO: patent foramen ovale; CABG: coronary artery bypass graft.
[a]Adjusted outcomes not reported for outcomes of interest.

between publications. Additional study-specific patient population characteristics are reported in Table 5.

Included observational study publications were of intermediate to high quality according to the Newcastle–Ottawa scale, with quality scores ranging from 5 to 8 out of a maximum of 9 points (Table 6).

Neurologic complications

Neurologic complications were reported in six publications, all of which were retrospective cohort studies (Table 1). There was no consistent definition of neurologic complications between publications (Table 2).

Table 4. Selected patient and operative characteristics by publication.

Publication	Age		Male		Vasculopathy		Cerebrovascular history		Bypass time		Clamp time	
	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP
Murzi et al.[8]	63 ± 13	60 ± 16	689 (48.5)	73 (51.8)	75 (5.0)	9 (6.4)	51 (3.4)	6 (4.3)	118 ± 13	113 ± 17	84 ± 16	81 ± 18
Barbero et al.[9,a]	69.2 ± 9.4	61.3 ± 13.9/67.1 ± 12.2	48 (76.2)	115 (48.3)/ 86 (57.3)	40 (63.5)	7 (2.9)/ 7 (4.7)	6 (9.5)	15 (6.3)/ 17 (11.3)	112.7 ± 21.6	132.9 ± 39.9/135.3 ± 42.7	84.7 ± 21.6	93.4 ± 25.3/93.5 ± 29.5
Bedeir et al.[12]	49 (43-55)	51 (45-55)	163 (50)	37 (65)	11 (3)	3 (5)	35 (11)	1 (2)	87 (68-114)	160 (140-207)	66 (51-83)	123 (93-149)
Murzi et al.[10]	63 ± 13	59 ± 14	615 (55.3)	84 (50.3)	67 (6.0)	11 (6.7)	66 (5.9)	9 (5.4)	136 ± 57	132 ± 53	95 ± 43	79 ± 43
Grossi et al.[1,b]	59.3		NR		3.20%		4.30%		NR		NR	
Ricci et al.[11,b]	61 ± 11		134 (55.6)		NR		NR		117 ± 46		71 ± 31	
Aklog et al.[13,b]	58.1 ± 12.7		62 (58.5)		NR		NR		152 ± 43		102 ± 35	

AAP: antegrade arterial perfusion; RAP: retrograde arterial perfusion; NR: not reported.
Values reported as mean ± SD, median (interquartile range), or n (%).
[a]Values for RAP split by clamp strategy (endoballoon/transthoracic clamp).
[b]Values not divided by perfusion strategy.

Table 5. Additional preoperative patient characteristics by publication.

Publication	Diabetes		COPD		Renal disease		BMI		Smoking		LVEF		Previous MI		Atrial fibrillation	
	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP	AAP	RAP
Murzi et al.[8]	125 (8.4)	11 (7.8)	119 (8.0)	14 (9.9)	45 (3.6)	4 (4.5)	NR		NR		57 ± 8	57 ± 10	NR		384 (34.5)	49 (29.3)
Barbero et al.[9,a]	4 (6.3)	28 (11.8)/ 11 (7.3)	5 (7.9)	20 (8.4)/ 10 (6.7)	7 (11.1)	23 (9.7)/ 10 (6.7)	25.1 ± 3.7	25.0 ± 4.8/24.3 ± 4.1	NR		56.8 ± 12.9	59.3 ± 10.8/61.2 ± 9.7	NR		19 (30.1)	94 (39.5)/ 52 (34.7)
Bedeir et al.[12]	38 (12)	7 (12)	NR		28 (7)	3 (5)	26 (23-31)	26 (23-29)	NR		60 (51-65)	60 (57-65)	NR		69 (21)	4 (7)
Murzi et al.[10]	116 (10.4)	12 (7.2)	105 (9.4)	17 (10.2)	37 (3.3)	4 (2.4)	NR		400 (35.9)	46 (27.5)	55 ± 9	54 ± 9	NR		49 (29.3)	384 (34.5)
Grossi et al.[1,b]	NR		8.3[c]		NR		NR		NR		4.3% with EF <30%		NR		NR	
Ricci et al.[11,b]	NR		NR		NR		NR		NR		NR		NR		95 (39.4)	
Aklog et al.[13,b]	NR		NR		NR		NR		NR		61 ± 12		NR		43 (41)	

COPD: chronic obstructive pulmonary disease; BMI: body mass index; MI: myocardial infarct; LVEF: left ventricular ejection fraction; AAP: antegrade arterial perfusion; RAP: retrograde arterial perfusion; NR: not reported; EF: ejection fraction .
Values reported as mean ± SD, median (interquartile range), or n (%).
[a]Values for RAP split by clamp strategy (endobaloon/transthoracic clamp).
[b]Values not divided by perfusion strategy.
[c]Only percentage reported.

Table 6. Quality assessment of included publications for the primary neurologic outcome (Newcastle–Ottawa scale).

Criteria for assessment	Adequately meets criterion	Murzi et al.[8]	Barbero et al.[9]	Bedeir et al.[12]	Murzi et al.[13]	Grossi et al.[1]	Ricci et al.[11]	Aklog et al.[13]
Selection								
Representativeness: exposed cohort	Clear selection/exclusion criteria for MIMVS	NS	Yes	Yes	NS	NS	NS	NS
Selection: non-exposed cohort	Drawn from the same community as the exposed cohort	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ascertainment of exposure	Secured surgical records	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome of interest not present at the start of the study	Reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Comparability								
Controls for most important factor	Yes, for patients with advanced atherosclerosis	No	Yes	No	No	No	No	No
Controls for other factors	Yes, adjustment model for comorbid conditions	Yes	Yes	Yes	Yes	Yes	No	No
Outcome								
Assessment of outcome	Objective assessment or medical record	Yes	No	No	Yes	Yes	No	No
Follow-up sufficiently long for outcome to occur	Within current hospitalization	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cohort follow-up adequate	Loss to follow-up <5%	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall score/9		7	8	7	7	7	5	5

MIMVS: minimally invasive mitral valve surgery; NS: not specified.

Three publications did not define what constituted a neurologic complication, nor was it reported how the complication was confirmed.[9,11,12] In two publications, a neurologic complication was defined as a new focal neurologic deficit assessed by the daily care physician, with specialist confirmation by a neurologist and imaging.[8,10] Finally, one publication defined a neurologic complication as a new permanent deficit, a transient deficit lasting greater than 24 hours, or a new lesion on cerebral imaging.[1] Adjusted ORs were reported in four publications. One publication required the calculation of the OR/95% CI, and one publication had zero events in one comparison group. All publications reporting adjusted ORs demonstrated results favoring antegrade perfusion for the risk of neurologic events (Figure 2).

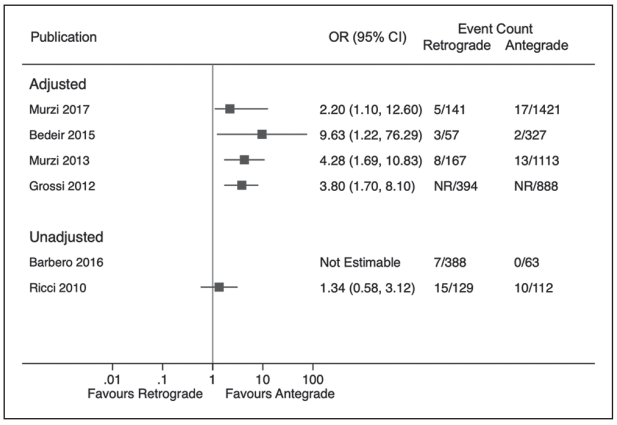

Figure 2. Risk estimates for neurologic events from six publications.

Mortality

Mortality was reported in five publications, with four retrospective cohort studies and one prospective cohort study (Table 1). Mortality was defined as mortality within 30 days in four publications (Table 2) [8–10,12] Operative mortality was reported in the remaining study.[13] An adjusted OR was reported in a single publication. A univariable OR was reported in one publication, while one publication required calculation of the OR/95% CI.[8,9] Mortality ORs from two publications were unable to be calculated due to zero-event groups. There was no clear pattern suggesting that mortality was influenced by perfusion strategy (Figure 3).

Renal failure

Renal failure was reported in four publications, all of which were retrospective cohort studies (Table 1). There was no consistent definition of renal failure between publications (Table 2). Two publications defined renal failure as acute kidney injury (AKI) with new hemodialysis or serum creatinine >200 μmol/L.[8,10] Renal failure was defined as new hemodialysis in one publication.[9] The final publication left renal failure undefined.[12] Adjusted ORs were reported in two publications.[10,12] One publication reported a univariable OR, and one required calculating the OR and 95% CI. When analyzing the data, two

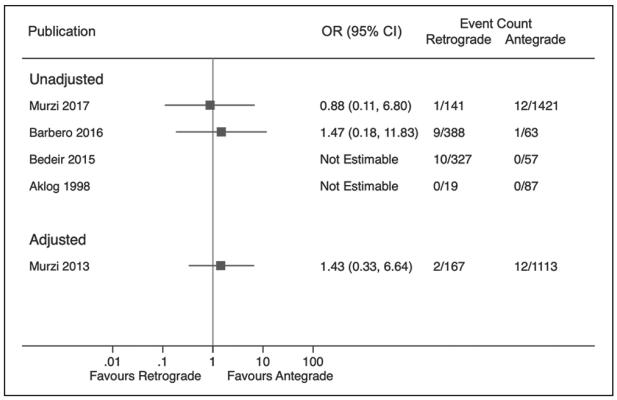

Figure 3. Risk estimates for 30-day mortality from five publications.

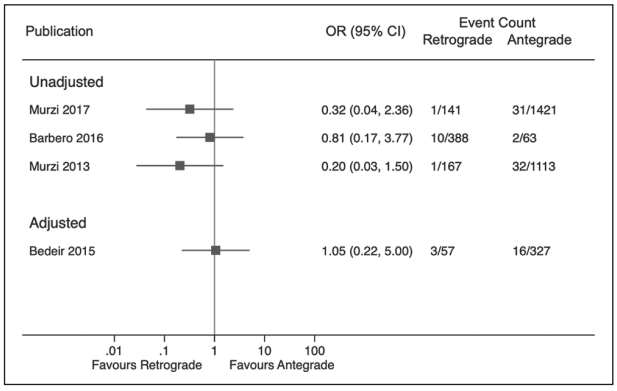

Figure 4. Risk estimates for renal failure from four publications.

publications were identified where the OR and 95% CI were incorrectly reported, with the OR being outside the range of the 95% CI.[8,10] For these publications, the renal failure OR/95% CI had to be derived from the reported event counts, rather than the reported univariable and adjusted OR/95% CI respectively. Therefore, one adjusted and three unadjusted estimates are reported. There was no clear pattern suggesting that renal failure was influenced by perfusion strategy (Figure 4).

Discussion

We performed a systematic review of observational studies comparing neurologic, mortality, and renal outcomes for patients undergoing MIMVS. Our results have demonstrated a possible association between retrograde arterial perfusion and neurologic complications in MIMVS. No clear association was evident between perfusion strategy and short-term mortality or renal failure. Consistent with our results, this lack of influence of perfusion strategy on renal failure and mortality has been previously demonstrated when considering all cardiac surgical procedures.[14] Considerable methodological heterogeneity was identified between publications.

When considering differences in operative and patient characteristics, results did not display consistency between publications (formal statistical analysis of this was beyond the scope of this study). Increased cardiopulmonary bypass and aortic clamp times did not consistently correlate with adverse outcomes. With retrograde perfusion, Barbero et al.[9] demonstrated increased cardiopulmonary bypass and aortic clamp times, but failed to demonstrate a difference in neurologic events. This was reported in the text of their publication stating an absence of risk factors for major neurological complications by multivariable analysis. Conversely, with retrograde perfusion, Bedeir et al.[12] demonstrated increased cardiopulmonary bypass and aortic clamp times with an increased adjusted risk of neurologic events. The two publications from Murzi et al.[8,10] showed comparable or lower bypass and clamp times, along with an increased adjusted risk of neurologic events, further confusing this potential relationship.

The single publication showing a major difference in the prevalence of vasculopathy between perfusion groups failed to demonstrate a difference in neurologic risk (Barbero et al.[9]). This is likely because this study used a specific preoperative protocol to image the patient's vasculature and define the best perfusion strategy. The International Society for Minimally Invasive Cardiothoracic Surgery provides clear recommendations for preoperative vascular assessment in this patient population, although the majority of the publications included in this review were published prior.[15] Patients with a higher aortic atherosclerotic burden are likely more prone to cerebral embolization given the retrograde direction of arterial flow into the cerebral vasculature, especially if aortic soft plaque is present. In a subgroup analysis, Murzi et al.[8] demonstrated an increased risk of neurologic events with retrograde perfusion in patients aged >70 years with a demonstrated atherosclerotic burden (OR = 6.4, 95% CI: 1.2-12.4, $p = 0.03$). Similarly, Grossi et al.[1] report an increased risk of neurologic events associated with retrograde perfusion in a high-risk aorta (OR = 8.5, $p = 0.04$). Additional publications have demonstrated results consistent with this, stressing the importance of vascular assessment. Though acknowledging the importance of assessment of the high-risk aorta, earlier publications have not recommended routine screening for all those considered for MIMVS.[3,16] However, a recent publication from the Cleveland Clinic demonstrated a decreased incidence of stroke from 2% to 0.8% ($p = 0.2$) after the institution of routine preoperative vascular imaging and risk stratification in robotic-assisted mitral valve surgery with retrograde perfusion.[17] Similarly, Lamelas et al.[18] have

reported fewer cerebrovascular events with retrograde perfusion compared with antegrade across a range of minimally invasive surgeries, including aortic and multi-valve procedures, after application of a preoperative vascular imaging protocol (1.17% vs. 2.6%, p = 0.088). This highlights the importance of patient selection, rather than perfusion strategy itself.

One important parameter varying between included publications was the use of the endoaortic occlusion balloon, potentially introducing a differential effect on the observed risk of neurologic complications. In a multicenter study from 2015, Casselman et al.[19] reported that an endoaortic occlusion technique does not impart excess neurologic risk in MIMVS. However, the reported incidence of neurologic complications was compared with existing literature and not a comparative study arm. In addition, all participating centers were highly experienced in the endoaortic technique and only contributed the most recent 50 consecutive cases, with each institution's first 50 being excluded. Biased results due to the elimination of learning curve effects in highly experienced centers cannot be excluded. Unfortunately, this study did not comparatively examine mortality or renal dysfunction in the context of endoaortic balloon use. More recently, Khan et al.[20] conducted a systematic review and meta-analysis examining endoaortic occlusion versus transthoracic aortic clamping. In this analysis, no difference in neurologic (pooled OR = 1.77, 95% CI: 0.65-4.8, p = 0.26), 30-day mortality (pooled OR = 0.69, 95% CI: 0.31-1.56, p = 0.37), or renal failure (pooled OR = 1.76, 95% CI: 0.36-8.59, p = 0.49) outcomes was demonstrated, although a higher risk of aortic dissection and conversion to sternotomy was noted in the endoaortic occlusion group. However, this meta-analysis was dominated by retrospective studies with allocation based on surgeon preference, introducing a high likelihood of selection bias. Given the inconclusive evidence on the effects of endoaortic occlusion on clinical outcomes, we cannot exclude a differential effect that has biased the results of our included publications as well as our analysis as a whole.

Strengths and limitations

Our current review was based on a systematic search of multiple databases, a reproducible search strategy with clear inclusion and exclusion criteria, a focus on primary mitral valve operations, and the performance of the search in duplicate with discussion over each included publication. Despite these strengths, publications may have been missed for inclusion, although we believe that with the comprehensiveness of the search strategy, the likelihood of this is low. We identified 10 potentially relevant publications that were abstracts with unpublished full text (gray literature), precluding the use of full results. This highlights the possibility of an existing publication bias.

Several important publications were ultimately excluded upon full-text review. In a recent review, consistent with previous reports, Lamelas et al.[18] reported a stroke incidence of 1.17% and 2.6% for retrograde and antegrade perfusion, respectively (p = 0.088), although approximately 50% of the population included minimally invasive aortic and/or aortic valve patients.[21] In a series comparing cannulation strategies, Chan et al.[2] reported an increased risk of a composite of stroke, prolonged intubation, renal failure, reoperation for bleeding, sepsis, myocardial infarction, and unplanned cardiac reoperation associated with peripheral cannulation (OR = 2.89, 95% CI not reported, p = 0.001). However, the study population was quite heterogeneous, with minimally invasive mitral surgeries making up only 66.4% of the population and three patients in the peripheral cannulation arm receiving axillary cannulation. Conversely, in a subgroup of mitral valve re-operative patients, Crooke et al.[22] demonstrated no difference in the crude incidence of stroke between perfusion strategies, although the intervention groups included both minimally invasive and conventional sternotomy approaches (2.9% for antegrade perfusion, 5.5% for retrograde perfusion, p = 0.15). Retrograde perfusion was, however, associated with an increased risk of stroke after multivariable regression modeling (OR = 4.4; 95% CI = 1.8-10.3, $p < 0.01$).

When considering any literature-based review, one must compare the summary output with the quality of the input publications. In the case of our study, all included publications were observational and often reported unadjusted data. In meta-analyzing observational data, it is likely, if not understood, that measured and unmeasured confounding factors will play a significant role. All input studies that were adjusted can only control for confounding by specific variables, which cannot capture everything, even in the most comprehensive adjustment model. In addition, variables not included or understood cannot be controlled for, which is the essential strength of a randomized study. Finally, only seven total publications were included, with relatively few outcome events. For these reasons, it was thought that performance of a meta-analysis was not appropriate given the data.

Related to, but distinct from, the issue of confounding is the issue of systematic error (bias), which cannot be controlled for after the fact. As all publications included were observational, they are all inherently susceptible to bias. Most concerning is the issue of selection bias, whereby a patient more likely to suffer a certain complication may be assigned to a treatment group where this complication may be less likely to occur. As all but one included publication were retrospective in

design, surgeon preference for cannulation strategy and surgical approach was likely influenced by the overall clinical condition of the patient. Of the three publications that defined group allocation criteria, only one publication included a protocol for evaluating which cannulation strategy was most appropriate based on preoperative imaging.[9] The effect of this intentional allocation should be to bias the results toward the null, which is what was observed for all three publications. This underscores the importance of patient-appropriate selection criteria for cannulation strategy rather than the influence of cannulation strategy itself. Two publications relied on surgeon's discretion and acknowledged an institutional shift in perfusion practice toward antegrade perfusion as well as differing surgical attitudes toward each perfusion strategy.[8,10] This could introduce differential group allocation between strategies, biasing results away from the null. Both of these publications demonstrated an increased neurologic risk with retrograde perfusion, but no difference in mortality or renal failure.

Although the results of this review have identified a relatively small number of publications, with relatively few outcome events in each, this still remains a synthesis of the best available evidence to answer our research question. The lack of a preoperative imaging protocol in all but one publication potentially explains the association between retrograde perfusion and neurologic complications. This is important for two specific reasons. First, sufficient controversy exists such that a clear direction for future study is identified. Second, the suggestion that the lack of a preoperative vascular assessment influences the neurologic risk is important for less experienced centers performing MIMVS without routine preoperative vascular screening.

Conclusion

This review has synthesized and discussed the best available evidence on the influence of perfusion strategy on selected clinical outcomes in MIMVS. A pattern of increased risk was demonstrated between retrograde arterial perfusion and neurologic events. There was no pattern of increased risk evident between retrograde arterial perfusion and 30-day mortality or renal failure. The lack of a preoperative imaging protocol in all but one publication potentially explains these results. Ultimately, these results identify uncertainty sufficient to justify further focused research.

Declaration of Conflicting Interests

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References

1. Grossi EA, Loulmet DF, Schwartz CF, et al. Evolution of operative techniques and perfusion strategies for minimally invasive mitral valve repair. *J Thorac Cardiovasc Surg* 2012; 143: S68–S70.
2. Chan EY, Lumbao DM, Iribarne A, et al. Evolution of cannulation techniques for minimally invasive cardiac surgery: a 10-year journey. *Innovations* 2012; 7: 9–14.
3. Modi P, Chitwood WR. Retrograde femoral arterial perfusion and stroke risk during minimally invasive mitral valve surgery: is there cause for concern. *Ann Cardiothorac Surg* 2013; 2: E1.
4. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation* 2017; 135: e1159–e1195.
5. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; 62: 1006–1012.
6. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
7. Schmitz C, Ashraf O, Bimmel D, et al. Direct aortic cannulation in minimally invasive mitral-valve operations. *Heart Surg Forum* 2002; 5: 370–372.
8. Murzi M, Cerillo AG, Gasbarri T, et al. Antegrade and retrograde perfusion in minimally invasive mitral valve surgery with transthoracic aortic clamping: a single-institution experience with 1632 patients over 12 years. *Interact Cardiovasc Thorac Surg* 2017; 24: 363–368.
9. Barbero C, Marchetto G, Ricci D, et al. Right minithoracotomy for mitral valve surgery: impact of tailored strategies on early outcome. *Ann Thorac Surg* 2016; 102: 1989–1994.
10. Murzi M, Cerillo AG, Miceli A, et al. Antegrade and retrograde arterial perfusion strategy in minimally invasive mitral-valve surgery: a propensity score analysis on 1280 patients. *Eur J Cardiothorac Surg* 2013; 43: e167–e172.
11. Ricci D, Pellegrini C, Aiello M, et al. Port-access surgery as elective approach for mitral valve operation in re-do procedures. *Eur J Cardiothorac Surg* 2010; 37: 920–925.
12. Bedeir K, Reardon M, Ramchandani M, et al. Elevated stroke risk associated with femoral artery cannulation during mitral valve surgery. *Semin Thorac Cardiovasc Surg* 2015; 27: 97–103.
13. Aklog L, Adams DH, Couper GS, et al. Techniques and results of direct-access minimally invasive mitral valve

surgery: a paradigm for the future. *J Thorac Cardiovasc Surg* 1998; 116: 705–715.
14. Saadat S, Schultheis M, Azzolini A, et al. Femoral cannulation: a safe vascular access option for cardiopulmonary bypass in minimally invasive cardiac surgery. *Perfusion* 2016; 31: 131–134.
15. Ailawadi G, Agnihotri AK, Mehall JR, et al. Minimally invasive mitral valve surgery I: patient selection, evaluation, and planning. *Innovations* 2016; 11: 243–250.
16. Yaffee DW, Galloway AC, Grossi EA. Editorial analysis: impact of perfusion strategy on stroke risk for minimally invasive cardiac surgery. *Eur J Cardiothorac Surg* 2012; 41: 1223–1224.
17. Gillinov AM, Mihaljevic T, Javadikasgari H, et al. Early results of robotically assisted mitral valve surgery: analysis of the first 1000 cases. *J Thorac Cardiovasc Surg* 2018; 155: 82–91.
18. Lamelas J, Williams RF, Mawad M, et al. Complications associated with femoral cannulation during minimally invasive cardiac surgery. *Ann Thorac Surg* 2017; 103: 1927–1932.
19. Casselman F, Aramendi J, Bentala M, et al. Endoaortic clamping does not increase the risk of stroke in minimal access mitral valve surgery: a multicenter experience. *Ann Thorac Surg* 2015; 100: 1334–1339.
20. Khan H, Hadjittofi C, Uzzaman M, et al. External aortic clamping versus endoaortic balloon occlusion in minimally invasive cardiac surgery: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2018; 27: 208–214.
21. LaPietra A, Santana O, Mihos CG, et al. Incidence of cerebrovascular accidents in patients undergoing minimally invasive valve surgery. *J Thorac Cardiovasc Surg* 2014; 148: 156–160.
22. Crooke GA, Schwartz CF, Ribakove GH, et al. Retrograde arterial perfusion, not incision location, significantly increases the risk of stroke in reoperative mitral valve procedures. *Ann Thorac Surg* 2010; 89: 723–730.

Review

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Euthyroid sick syndrome in paediatric and adult patients requiring extracorporeal circulatory support and the role of thyroid hormone supplementation: a review

Beatriz Nistal-Nuño

Abstract

Non-thyroid disorders may modify thyroid hormone metabolism, resulting in an 'euthyroid sick syndrome'. Studies determining the association of cardiopulmonary bypass to thyroid function showed changes in line with this euthyroid sick syndrome. In some cases, cardiovascular dysfunction after cardiac surgery with cardiopulmonary bypass is comparable to that noticed in hypothyroidism associated with low cardiac output and elevated systemic vascular resistance. Numerous lines of research have proposed that triiodothyronine can behave acutely as a positive inotropic and vasodilator agent. The aim of this review is to present an update on the current literature about in what clinical situations the use of thyroid supplementation during the perioperative period of extracorporeal circulation in the adult and paediatric populations may impact outcome to any appreciable degree. The contribution of thyroid function in patients undergoing a ventricular assist device implantation is additionally reviewed and future study directions are proposed. This is a narrative review, where the search strategy consisted on retrieving the articles through an extensive literature search performed using electronic databases from January 1978 up to September 2019. All controlled trials randomly allocating to perioperative thyroid hormone administration in children and adults undergoing extracorporeal circulation for cardiac surgery were considered. Thyroid hormone supplementation may be recommended particularly in selected paediatric sub-populations. There is currently no firm evidence regarding the benefits of routine use of thyroid hormone administration in cardiac adult patients. Further studies are required to assess the beneficial effect of thyroid hormone on patients with end-stage heart failure supported by ventricular assist devices.

Keywords

cardiopulmonary bypass; euthyroid sick syndrome; cardiac surgery; ventricular assist device; triiodothyronine

Introduction

The consequences of thyroid hormones on the cardiac and peripheral vascular system are well known.[1] Pathologic changes in cardiovascular function occur in the presence of chronic hypothyroidism and hyperthyroidism.[2,3] Thyroid hormone metabolism can be altered as a result of numerous non-thyroidal disorders, such as brain death, sepsis, congestive heart failure, cardiopulmonary bypass (CPB), cardiac transplantation, myocardial infarction, amiodarone therapy and cardiopulmonary arrest, which eventually lead to the development of the 'euthyroid sick syndrome' (ESS) or low triiodothyronine (T3) syndrome. Discussion has concentrated on whether these alterations are adaptive or possibly unfavourable, and whether treatment to return T3 levels to normal is advisable.[4,5] One of the objectives of this review is to study the changes in the levels of thyroid hormones characteristic of the ESS during extracorporeal circulation by reviewing the important literature on the development of ESS in paediatric and adult patients, and to study the thyroid function changes in patients with chronic heart failure requiring a ventricular assist device (VAD) placement.

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Numerous lines of research have proposed that T3 can behave acutely as a positive inotropic and vasodilator agent. The use of thyroid supplementation during the perioperative period of cardiac surgery or extracorporeal circulation in the adult and paediatric population has encouraged anecdotal reports over the years. The aim of this review is also to present an update on the current literature about in what clinical situations this may impact outcome to any appreciable degree. Scarce literature exists regarding thyroid function during and post-VAD, studying the impact of the low T3 state. The contribution of thyroid function in patients at risk of postoperative cardiac dysfunction such as those undergoing a VAD insertion is additionally reviewed and future study directions are proposed.

There is not enough uniformity in the assessment and treatment of transient secondary hypothyroidism perioperatively in CPB patients. Many trials have been conducted with conflicting results. There are some reviews about thyroid hormone supplementation in adult cardiac surgery, with the latest from the year 2010. The consensus statement about thyroid pharmacotherapy from the Pediatric Cardiac Intensive Care Society is from the year 2014. This work is the latest review to date to present an updated summary of the evidence, particularly of relevant literature of randomized controlled trials of T3/T4 supplementation in adult and paediatric cardiac surgery with their findings. A comprehensive review of the current literature is provided covering the above-mentioned topics, and the findings are summarized for a recommendation.

Methods

The search strategy of this narrative review consisted on retrieving the articles through an extensive literature search performed using the electronic databases of Medline, Scopus, Google Scholar, Embase, and the Cochrane Library from January 1978 up to September 2019 in the English language. The search terms were keywords relevant to the topics under study, such as 'cardiac surgery', 'cardiac critical care', 'adults', 'children', 'euthyroid sick syndrome', 'thyroid hormones', 'trial', 'ventricular assist device', and 'review'. Particular emphasis was given to implications of the ESS on patients undergoing cardiac surgery requiring extracorporeal circulation. All controlled trials randomly allocating to perioperative thyroid hormone supplementation compared to a control group in children and adults undergoing cardiac surgery requiring CPB were considered for review. Primary clinical outcomes were the focus, including measures of postoperative morbidity and mortality, but secondary outcomes were included also if relevant.

Physiology

Normal physiology of thyroid function

Two hormones, thyroxine (T4) and T3, are elaborated by the thyroid gland. The predominant constituent of thyroid hormone is T4, which functions principally as a prohormone. Thyroid hormone biosynthesis and release by the thyroid follicles is adjusted by the hypothalamic thyrotropin-releasing hormone (TRH), which triggers the biosynthesis and secretion of thyroid-stimulating hormone (TSH) that, sequentially, adjusts thyroid hormone concentrations. Nearly all T4 is transformed to biologically active T3 via the elimination of an iodide by deiodination, a peripheral process. While there are three kinds of deiodinases, nearly all circulating T3 is obtained from Type 1 deiodinase; Type 1 deiodinase activates thyroid hormone by transforming T4 to active T3 and inactivates thyroid hormone by transforming T4 to inactive reverse T3 (rT3). Since there is no appreciable intracellular deiodinase function in myocytes, the heart depends mainly on the action of T3. T4 and T3 are in the blood almost fully (>95%) bound to thyroxine-binding globulin (TBG) and other hormone-binding proteins.[3]

Hyper- and hypothyroid states and their cardiovascular effects

Hypothyroidism is identified when low thyroid hormones result in increased levels of TSH, while subclinical hypothyroidism is identified when TSH levels are increased above the upper reference range with normal thyroid hormone levels. Thyroid hormones have a substantial function in the normal cardiac and vascular physiology.[2]

Hypothyroidism is associated with reduced cardiac output (CO) due to impaired relaxation of vascular smooth myocytes and reduced accessibility of endothelial nitric oxide. This induces a cascade effect of increased arterial stiffness that leads to elevation in systemic vascular resistance (SVR). Thyroid hormones additionally affect the renin-angiotensin-aldosterone system, stimulating the elaboration of renin substrates in the liver. Therefore, in a hypothyroid state, diastolic blood pressure increases, pulse pressure narrows, and renin levels decrease. Thyroid hormones control pacemaker-related genes via transcription as well as the beta-adrenergic system in cardiac cells. As a consequence, heart rate decreases in hypothyroidism. Thyroid hormones affect endothelial functions via thyroid hormone receptors (THR). Activation of THR-α1 augments coronary blood flow and increases biosynthesis of nitric oxide in endothelial and vascular smooth myocytes (Figure 1).[2]

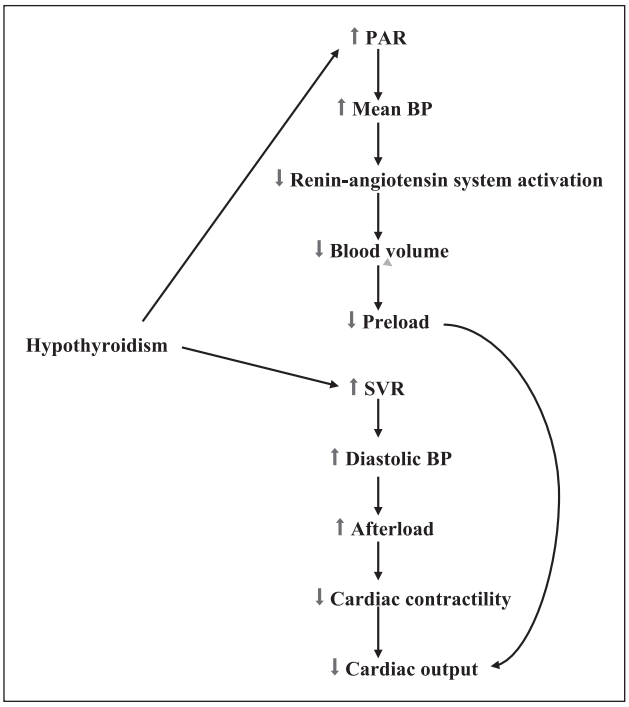

Figure 1. Cardiovascular consequences of hypothyroidism. SVR: systemic vascular resistance; BP: blood pressure; PAR: peripheral arterial resistance.

Hyperthyroidism increases resting heart rate, blood volume, stroke volume, myocardial contractility, ejection fraction (EF) and diastolic relaxation, which is analogous to a situation of increased adrenergic function. In thyrotoxicosis, plasma catecholamines are normal or low, and the β-adrenergic receptor density is modified, eliciting an elevated tissue sensitivity to catecholamines. In addition to the elevated levels of β-1 adrenergic receptors and guanosine triphosphate–binding proteins, thyroid hormone reduces the expression of cardiac-specific adenylyl cyclase catalytic subunits and preserves cellular reaction to β-1 adrenergic agonists within ordinary limits. Thus, a β-adrenergic receptor antagonist in hyperthyroidism slows the heart rate but does not change systolic or diastolic myocardial contraction, proposing that the positive inotropic outcome of T3 is unrelated to adrenergic signalling pathways. T3 elevates the rates of depolarization and repolarization of the sinoatrial node, increasing heart rate (Figure 2).[3]

The low T3 syndrome

Patients with critical illnesses who need treatment in the intensive care unit (ICU) regularly show alterations in plasma thyroid hormone levels that are named as ESS.[6] In contrast to classic hypothyroidism, these patients have normal to increased free T4 (fT4) levels, normal to decreased T4 concentrations, reduced free and total T3,

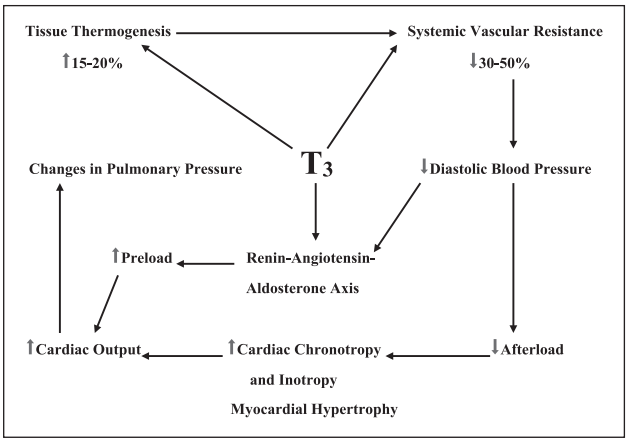

Figure 2. Cardiovascular consequences of hyperthyroidism.

typically inappropriately low or normal TSH levels and elevated serum rT3 levels. The most prominent alteration in ESS is low serum T3 concentration.[5–7]

Besides these changes in thyroid hormones, there are changes in the core adjustment of the thyroid axis reducing the capacity of the pituitary to secrete TSH, as well as changes in the peripheral components of the thyroid axis. These peripheral changes may vary per tissue, per class and severity of disease.[6,7] Four suggested mechanisms may explain the pathogenesis of this syndrome. First, the reduced extra-thyroidal conversion of T4 into T3 following the reduced delivery of T4 to the intracellular deiodinases or a reduction in the deiodinase activity. Impaired deiodination results in a reduction of total T4 and T3 levels and an elevation in rT3.[5] Second, a reduction in thyrotropin secretion leading to a decrease in thyroidal secretion of T4 and T3. This enhances the decrease in T4 serum concentration, therefore generating less substrate for T3 transformation.[5] Third, the production of TBG, transthyretin and albumin or their affinity for thyroid hormones may decrease.[5] Fourth, tissue captation of T4 and T3 may be reduced, in addition to reduced nuclear and post-receptor hormone actions.[4–6]

The ESS that occurs in reaction to critical illnesses could be adaptive, to reduce metabolic demands during the stress of non-thyroidal disease, or alternatively maladaptive. This alternative perspective is that these alterations in thyroid hormone metabolism may contribute to the disease rather than derive from it.[7] This interpretation is based on the observation that the magnitude of the alterations in plasma thyroid hormones is related to the risk of detrimental outcomes, most commonly mortality, in subjects with non-thyroidal disease.[6,7] Since pump oxygenators cause an inflammatory response, it is presumed that the ESS may be associated to this inflammatory response.[7] CPB has been considered as an established cause of ESS in the literature.[6,8]

Thyroid hormones and implications in extracorporeal circulatory support

The consequences of CPB on thyroid function

Pathological phenomena associated with CPB, like endothelial injury, ischaemia-reperfusion (IR), and particularly liberation of cytokines, adhesion molecules and tissue necrosis factor, can alter the homeostasis among biochemical, hormonal and cellular processes. Research has demonstrated that endothelial dysfunction during CPB is caused mainly by the interaction among neutrophils and inflammatory molecules through activated endothelium, producing an inadequate control of the trans-endothelial transfer of neutrophils.[9]

The thyroid hormonal consequences associated to CPB have been assessed in recent decades.[10] Studies have demonstrated that in adults undergoing CPB, serum total and free T3 levels diminish significantly in 50 to 75% of patients in the immediate perioperative period.[4,7] This reduction continues for 1 to 4 days postoperatively.[5] The process by which T3 levels decrease was initially related to hypothermia, haemodilution, caloric deprivation, and the activation of inflammatory response mediators including IL-6. This may result in less peripheral transformation of T4 to T3, modified volume of distribution, and a shortened half-life of T3.[4,11]

Holland et al. evaluated 14 adult patients to determine the effect of CPB on the levels of thyroid hormones and metabolites. They observed that the most important effects of CPB on the levels of thyroid hormones were noticed 2-24 hours following surgery, corresponding to an interval when low CO syndrome and haemodynamic instability are regularly observed. The data indicated a considerable decrease in total T3 (TT3) and free T3 (fT3) concentrations to well under normal physiological range after CPB.[12]

Keceligil et al. evaluated 20 patients aged 2-63 years to study the association of CPB to alterations in thyroid function. Blood samples were obtained preoperatively, and at particular times before, during and following CPB. This study revealed a remarkable reduction in TT3, total T4 (TT4) and fT3 concentrations well under the normal physiological range during and following CPB. They deduced these alterations were probably secondary to modifications in thyroid hormone metabolism, and not to just uptake and degradation by the extracorporeal circuit or haemodilution. They suggested that either peripheral conversion of T4 to T3 may be decreased as part of the metabolic response to bypass or that utilization of T3 is significantly augmented. Conversely, serum TSH and fT4 concentrations did not manifest significant changes during and following CPB. Changes in TT3, TT4 and fT3 levels were compatible with the ESS.[13]

Comparable results have been found also in infants. Plumpton et al. studied 36 infants undergoing CPB for congenital heart surgery. Thyroid hormones were analysed on admittance to the ICU and on postoperative days 1 and 2. Increased CPB time was associated with reduced admission fT3 and TSH levels. Infants who continued to need ventilation 48 hours after ICU admittance showed a mean fT3 concentration on postoperative day 2 that was lower than in those who had been extubated.[14,15]

Gabriel et al. assessed the hormonal effect of CPB for coronary artery bypass grafting (CABG). Their results showed a reduction in serum TT3 and fT3, particularly during the initial 24 hours postoperatively. They observed a similar behaviour in the serum TT4. However, the serum levels of fT4 were stable immediately after termination of CPB.[9] The prognostic importance of the ESS on the outcome of patients undergoing CABG with CPB was evaluated by Cerillo et al. Their study demonstrated that low T3 is a robust predictor of mortality and decreased CO in CABG patients. They recommended that individuals with low T3 should be deemed at higher risk.[16]

Off-pump coronary artery bypass (OPCAB) has been considered to be less invasive than CABG with CPB (ONCAB). Cerillo et al. compared thyroid hormones in 9 patients undergoing ONCAB to 11 patients undergoing OPCAB. OPCAB induced an ESS similar to that observed after CPB. This finding suggested that ESS is a non-specific reaction to stress. They concluded CPB should not be considered as the unique trigger of ESS in cardiac surgical patients.[8] Keeping with similar observations is the study of Velissaris et al.,[11] who studied 52 low-risk patients undergoing CABG, randomized into either ONCAB or OPCAB categories. They found the thyroid hormone changes during OPCAB were comparable to those after CPB and consistent with the ESS. They argued whether these findings would be relevant in high-risk patients. Their review revealed that the unique significant factor related to CPB was the use of pulsatile or non-pulsatile flow during CPB, reducing the factors that determine thyroid axis response to haemodynamic factors and the stress of surgery.[11]

Change in thyroid function during extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is the most frequently utilized mechanical circulatory assistance in infants and children and is increasingly being used in adults with cardiac and respiratory failure. This support offers haemodynamic rescue and/or a bridge to

myocardial recovery after damage caused during congenital heart surgery or other cardiac injuries.[17] Unfavourable events and death are associated directly to the duration of mechanical support. ECMO provokes a substantial surge in pro-inflammatory cytokines, which can detrimentally affect cardiac function and retard weaning. Increases in particular cytokines are directly comparable to substantial reduction in T3 concentrations produced by mechanical circulation.[17–19]

Thyroid function changes in patients without cardiac illness on ECMO have been formerly reported. Stewart et al.[7] studied the temporal association among changes in thyroid hormones and ECMO in non-cardiac infants with intractable respiratory failure, and whether these alterations anticipated outcomes. They found that the decrease in all thyroid hormones measured in the survivors was statistically significant in contrast to baseline, and recuperation was total. However, in the non-survivors, the decline was not statistically significant. Recuperation of the thyroid hormones in the survivors had started before ECMO was terminated, whereas in the non-survivors, never augmented. Thyroid function variations noted during ECMO were compatible with the ESS. It was speculated that the optimal adaptive response is not only a thyroid shutdown, where all compensatory mechanisms are inhibited causing a drop in serum T3 levels, but the fast recovery of thyroid function. That is why sustained or recurrent depression of thyroid function resulted in death for the patients of the study of Stewart et al.[7]

Leeuwen et al. conducted a study in order to investigate whether ECMO has an impact on congenital hypothyroidism (CH) screening results. Analysis of the screening results can be confused by states generating an ESS such as prematurity, drug utilization, cardiac surgery, and critical disease. They found that anomalous CH screening results were noted in most ECMO-treated neonates, being presumably attributable to ESS.[20]

The role of thyroid hormone administration in the context of extracorporeal circulation

In some cases, cardiovascular dysfunction after cardiac surgery with CPB is comparable to that noticed in hypothyroidism with regard to low CO and elevated SVR.[4,10] Numerous lines of evidence have proposed that T3 can behave acutely as a positive inotropic and vasodilator agent.[4,5] The principal origin of perioperative mortality and goal for further improving outcome following CPB is low-output cardiac failure. Preliminary clinical experience proposed that the administration of T3 to patients undergoing CABG surgery enhanced haemodynamic performance and overall outcome.[4,21–23] This anecdotal experience produced further experimental and prospective, randomized clinical trials.[18,24–34]

Initial animal studies revealed that repletion of T3 enhanced postischemic ventricular recovery in injured hearts.[5,35] Dyke et al.[36] additionally assessed the consequences of postischemic T3 repletion in the large animal CPB model. Remarkable enhanced recuperation of left ventricular contractility was observed in the T3-treated group at 90 and 120 minutes after re-perfusion.[36] Data from these studies have proposed a mechanism different from that anticipated from traditional cardiac inotropic agents. T3 had no recognizable effect on the function of normal, uninjured myocardium while it improved contractility in postischemic hearts without harmful effects on myocardial oxygen consumption.[12] The capacity of T3 to decrease peripheral vascular resistance directly has been assessed in a number of lab settings. Dipierro and colleagues revealed that T3 enhanced cardiac performance in an in vivo sheep model by acutely lowering SVR. Acute increments in coronary artery flow have been detailed as well.[37]

In the adult population. Clinical experience with T3 and cardiac surgery was first detailed in two small trials by Novitzky and colleagues. T3 was administered to 12 patients encountering difficulty weaning from CPB or in whom low CO was unresponsive to inotropic or intra-aortic balloon pump support. In subjects with a left ventricular ejection fraction (LVEF) of less than 30%, T3 administration was associated with a significantly decreased need for inotropic agents. In patients with a LVEF greater than 40%, T3 administration resulted in significantly enhanced stroke volume and CO and decreased systemic and pulmonary vascular resistances.[38]

This introductory experience was followed by large-scale, well-controlled trials in adults and children.[24,29–31,39–42] In a prospective, randomized investigation of 142 high-risk CABG patients, T3 was administered at aortic cross-clamp removal followed by uninterrupted infusion for the next 6 hours. T3-treated patients had higher CO and lower SVR.[23] However, there was no difference in requirement for inotropic support in the initial 24 hours and no difference in mortality or arrhythmias among the two groups.[23] Analogous haemodynamic findings were described in a similar investigation of 170 patients undergoing elective CABG. T3 administration resulted also in higher CO, but unlike the previous study, it reduced dependence on inotropic agents, and it caused a reduced incidence of atrial fibrillation.[22]

In heart transplantation. As a product of the accompanying non-thyroidal illness, low T3 levels are present in most heart transplantation (HT) donors and recipients and may be a factor in donor heart dysfunction following HT. The administration of T3 to brain-dead organ

donors was among the initial clinical applications of parenteral T3 therapy, aimed at enhancing haemodynamic performance and improving organ retrieval. Considering the limited number of organ donors, thyroid hormone therapy constitutes an element of donor stabilization at some transplant units in order to achieve optimal conditions for the available organs.[43,44]

Data on 63,593 donors of hearts and lungs were retrospectively examined by Novitzky et al.[45] T3/T4 treatment to the donor was related to either enhanced post-transplant graft and recipient survival or no variation in survival, indicating a remarkable favourable impact on heart and lung retrieval independent of other factors. Kumar et al. assessed the impact of T3 on the performance of the immature donor heart in an animal model. Contrarily, post-CPB survival durations were inversely associated with the ischaemic durations in both arms, which were not influenced by T3. There was no variation in inotropic score, EF, biochemical analyses, myocardial performance or survival among the two arms.[44]

In the paediatric population. Some studies in infants[30] reveal that T3 administration enhances cardiac function after the IR damage of CPB. Files et al. studied these outcomes in a swine model, mimicking infant ECMO for cardiac support. They noted that thyroid hormone administration permitted better functional recuperation with almost complete rehabilitation of the metabolic parameters, supporting the ability of thyroid hormone in enhancing weaning from ECMO. T3 supplementation significantly increased left ventricular systolic and diastolic pressure when weaning after ECMO. This was not observed in the control group.[17]

The study of Chowdhury et al.[46] showed a substantially lower therapeutic intervention scoring system (TISS) score, lower inotropic requirements and increased MVO2 in newborns compared to older paediatric patients. The studies of Marwali et al. and the Triiodothyronine supplementation in infants and children undergoing CPB (TRICC) trial found that T3 administration provides clinical advantages and reduces time to extubation (TTE) in patients younger than 5 months undergoing congenital heart disease surgery and no advantage for those older than 5 months.[29,31] The study of Zhang et al.[42] found that thyroid hormone significantly decreased the requirement of inotropic drugs in the ICU and provided protection against myocardial IR injury in paediatric patients undergoing simple cardiac surgery with CPB. The study of Talwar et al.[40] showed that oral T4 improved the cardiac index, reduced inotropic requirements, the duration of mechanical ventilation, ICU stay, and TISS in infants after surgery for complex congenital heart defects. This study concluded that the administration of T4 is more effective in the complex group of paediatric patients, but probably not needed in the simple patients.[40]

The following table represents all the relevant citations to date of randomized controlled trials of T3/T4 supplementation in adult and paediatric cardiac surgery (Table 1). The benefit of T3 supplementation for cardiac function and inotropic support in the postoperative period, the postoperative mortality rate, TTE, length of stay and postoperative atrial fibrillation have been studied. Rarely were any unfavourable effects of exogenous T3 administration observed. The primary outcomes are noted to clarify if the findings are related to primary or secondary outcomes.

In summary, the low T3 state produced from CPB can be safely reversed. Early postoperative haemodynamic performance is enhanced, and a decrease in the incidence of postoperative atrial fibrillation has been proposed.[4,22] While most randomized investigations do not conclusively reinforce the regular administration of T3 to patients undergoing CABG surgery, the favourable effects on postoperative haemodynamics and myocardial ischaemia propose that a possible role does exist, mostly in patients labelled at high risk of postoperative cardiac dysfunction. Among these patients are those undergoing a left ventricular assist device (LVAD) implantation.

Past studies involving VADs

Regarding the heart failure and VAD population, to date, only a few small prospective studies have been performed to assess thyroid function during and post insertion of a VAD. Ito et al. concluded from an animal experiment that prolonged mechanical cardiac unloading, as it occurs in patients with end-stage heart failure following LVAD implantation, is related to altered expression levels of Ca2+ cycling-related proteins, myosin heavy chain (MHC) isoform shift and worsened cardiac performance. Treatment with the physiological dose of thyroid hormone has a possibility to re-establish calcium handling and contractile function in chronically unloaded hearts. These considerations suggest clinical implications in the future for the management of patients with end-stage heart failure supported by LVAD, although these are conclusions from animal experiments and future studies are required to clarify other possible mechanisms of the beneficial effects.[47]

Noirhomme et al. investigated six patients who had implantation of a Novacor for end-stage heart failure. The Novacor LVAD is a first-generation, portable, electric, dual pusher plate device designed for long-term cardiac support. They assessed neuroendocrine activation measuring serum aldosterone, renin, cortisol, testosterone and thyroid hormones. Samples were collected immediately prior to LVAD implantation and up to 90 days after. Plasma T3 was considerably lower than normal pre-implantation. The restitution of T3 to normal levels was seen after 90 days of support. This

indicates that the monitoring of this latent period previous to metabolic recovery maybe is a major parameter to contemplate, along with quantification of cardiac recovery, before weaning the device in specific patients with correctable cardiomyopathy.[48] However, this needs further study because it included only six patients and this concept was not the main conclusion of the study. This device has been discontinued currently.

Wieselthaler et al. studied the effect of continuous pulseless Micro-Med-DeBakey axial flow pumps on the endocrine function in nine patients. After an average period of 67 + 19 days, basal pituitary hormone levels and their responses to a bolus administration of TRH were evaluated. Peripheral thyroid hormones (T4, T3, fT4 and fT3) and their binding proteins were in the normal range. The short-term effect of LVAD on thyroid function was not evaluated. However, new LVAD devices that work through different methodology to this DeBakey device have not been thoroughly assessed.[49] Furthermore, this study is considerably underpowered, as is the one of Noirhomme et al.

Adamopoulos et al. studied 22 heart failure patients implanted with either intra-corporeal LVAD or extra-corporeal LVAD or bi-ventricular assist device (BiVAD; Berlin Heart GmbH, Berlin, Germany) as a bridge to HT. They investigated whether changes in thyroid hormone signalling can happen in the unloaded, failing myocardium in reaction to physical training. TT3, TT4 and TSH levels were analysed in all individuals at pre-VAD and pre-HT stages. They found that unloaded failing myocardium reacted to physical training by amplifying thyroid hormone signalling. Nevertheless, this response may not be enough to conduct to total recuperation.[50]

'Gaps in Knowledge' and proposed future study directions

Scarce literature exists regarding thyroid function during and post-VAD, studying the impact of the low T3 state for the implantation of a VAD. Therefore, there are many questions that are still unanswered. The anti-arrhythmic agent amiodarone is responsible for the most confusing effects on thyroid function. This is due to at least three underlying mechanisms: inhibition of T4 to T3 conversion, iodine overload, and direct toxic effects on thyroid tissue. Inhibition of conversion leads to increased T4 and decreased T3 levels in the majority of patients without any thyroid disease and directly stimulates TSH secretion.[51–54]

Despite most patients requiring a LVAD have an implantable cardioverter defibrillator or pacemaker to control the rhythm and to protect against tachyarrhythmia, amiodarone plays a significant role in the perioperative management of many of these patients. Many of these patients will be on amiodarone therapy as a result of the high incidence of arrhythmias in this patient population. There is insufficient literature about amiodarone in these patients. Only a few cases of LVAD have been studied, for example, thrombosis potentiated by amiodarone-induced hyperthyroidism.[55] Of note, the precise impact of CPB on amiodarone levels is not well understood. As a result, one of the areas of research that would need to be evaluated is the impact of CPB on amiodarone levels in this patient population. It should also be evaluated the effect of amiodarone on thyroid performance in these patients.[51–54]

In relation to the above insights, it would be interesting to thoroughly determine the impact of the low T3 state that occurs during and following CPB in patients undergoing implantation of a LVAD. This could be addressed by comparing the levels of thyroid hormones with the haemodynamic performance and incidence of arrhythmias in the postoperative period of patients undergoing CPB for LVAD implantation. Another question to consider is T3 as a marker for weaning. To ascertain the association (if any) between changes in thyroid hormone levels and patient outcomes, the postoperative and mid-term morbidity after CPB should be evaluated, accounting for clinical demographic information and preoperative INTERMACS score of the LVAD patients. In addition, defining the impact of CPB on the levels of thyroid hormones in patients undergoing insertion of a LVAD before, during and following CPB. Finally, the effect of CPB on amiodarone levels should be ascertained, in addition to the impact of amiodarone on thyroid function. The scope of future research should be broaden to discuss the role of T3/T4 also in the context of right ventricular assist device (RVAD), BiVAD and CPB complicated by postoperative cardiac dysfunction needing mechanical circulatory support.

Further research is needed regarding the significance of thyroid status in cardiovascular dysfunction following CPB. As the ESS is characterized by low CO and elevated SVR, its importance is arguable because nowadays in high proportion of cases the problem lies in low SVR. Post-CPB vasoplegia is characterized by hyperdynamic circulation and low SVR. Low CO with high SVR state after cardiac surgery with CPB is not uncommon but would not necessarily be related to CPB.

In addition to the studies of Cerillo et al. and Velissaris et al. that found thyroid hormone changes during OPCAB comparable to those after CPB and consistent with the ESS, a posterior trial by Choi et al.[24] found no differences between groups on haemodynamic variables and outcomes after T3 administration in adults undergoing elective OPCAB. Therefore, research would be needed to clarify these observations pertaining to OPCAB.

Table 1. Summary of relevant literature in chronological order of randomized controlled trials of thyroid hormone supplementation in adult and paediatric cardiac surgery and their principal results.

	Author	Year of publication	Patients (N)	Primary outcome	Principle positive findings	Principle negative findings
Adult population	Novitzky et al.[38]	1989	12	Inotropic agents and haemodynamic parameters in adults undergoing myocardial re-vascularization under CPB.	In patients with LVEF < 30%: a significantly reduced need for inotropic agents and diuretics. In patients with LVEF > 40%: significantly improved SV and CO and reduced SVR and pulmonary vascular resistance.	
	Klemperer et al.[23]	1995	142	Clinical and haemodynamic responses; need for inotropic or vasodilator drugs in adults undergoing CABG with CPB.	Significant increases in CO and decreases in SVR; increased early postoperative cardiovascular performance.	No difference in vasopressors, mortality, arrhythmia.
	Bennett-Guerrero et al.[34]	1996	211	Perioperative haemodynamic variables, inotropic support and serum T3 in high-risk adults undergoing CABG with CPB.	Prevents decreases in serum thyroid hormone associated with CPB; mild effects on myocardial performance.	T3 does not affect dramatically haemodynamic variables or inotropic drug requirements. Increased use of intra-aortic balloon counterpulsation.
	Mullis-Jansson et al.[22]	1999	170	Define the effect of T3 on haemodynamics and outcomes after elective adult CABG with CPB.	Higher CI and lower inotropic requirements; dramatically reduced incidence of postoperative myocardial ischaemia, pacemaker dependence and postoperative mechanical assistance; slightly decreased incidence of postoperative atrial fibrillation.	Improvements in CI were not observed in women.
	Carrel et al.[26] (no randomized trial)	2002	54 adults; 7 paediatric patients.	8 adult transplant candidates; 32 adult multi-organ donors; 3 adults during cardiac transplantation; 11 adults during CABG or valvular surgery with CPB; 7 paediatric patients for congenital heart surgery.	In 45 patients, stabilization of the haemodynamic situation with a decrease in inotropic support.	In 11 patients no beneficial effects were observed.
	Güden et al.[33]	2002	60	Serum T3 levels and haemodynamic parameters in adults undergoing CABG with CPB.	Mean postoperative CI was slightly higher; SVR was significantly lower.	No significant differences in the incidence of arrhythmia, the need for inotropic support, ICU stay, mortality, and morbidity.
	Sirlak et al.[25]	2004	80	Cardiac function, morbidity and mortality after elective CABG with CPB in adults with a preoperative LVEF less than 30%.	Higher CI; lower mean inotropic requirements.	No differences in mortality.
	Ranasinghe et al.[39]	2006	440	Cardiovascular performance and comparison of CI after on-pump CABG in adults.	T3 therapy significantly increased CI in the 6- to 12-hour period and at 12 hours after AXC removal; reduced inotropic requirements at 6 hours post AXC and reduced troponin I release; T3 improved haemodynamic performance.	Combination therapy including T3 did not provide added haemodynamic effect.
	Pingitore et al.[27]	2008	20	Electrocardiography, cardiac magnetic resonance and bio-humoral profile in patients with ischaemic or non-ischaemic DC.	Left-ventricular end-diastolic volume and SV increased; plasma noradrenaline, N-terminal pro-B-Type natriuretic peptide, and aldosterone significantly decreased.	External and intra-cardiac workload did not change.
	Choi et al.[24]	2013	100	Postoperative thyroid hormone concentrations, haemodynamic variables and outcomes in adult elective off-pump CABG.	Significantly attenuated the postoperative decline in T3 concentrations.	Haemodynamic variables, postoperative inotropic requirements and outcome variables showed no differences among the groups.

(Continued)

Table 1. (Continued)

	Author	Year of publication	Patients (N)	Primary outcome	Principle positive findings	Principle negative findings
Paediatric population	Portman et al.[30]	2000	14	Cardiac function reserve postoperatively in infants undergoing surgery for congenital heart disease.	Prevents circulating T3 deficiencies; promotes elevation in HR without concomitant decrease in systemic blood pressure; improves myocardial oxygen consumption; may enhance cardiac function reserve.	No significant differences among the two groups for systolic and diastolic pressures.
	Bettendorf et al.[28]	2000	40	Plasma concentrations of thyroid hormones, and systolic cardiac function; TISS; in children undergoing CPB surgery.	Raises T3 plasma concentrations and improves myocardial function; lower need for postoperative ICU; higher mean change of CI; significantly lower mean TISS.	
	Chowdhury et al.[46]	2001	75	Postoperative and long-term morbidity and mortality; in patients up to 18 years of age undergoing congenital heart disease surgery.	Newborns showed a significantly lower TISS and lower inotropic requirements; MVO2 in newborns increased by 17%, compared with a 2% increase in the control group.	Overall, no differences for TISS, inotropic score or dose requirements for milrinone and furosemide; no significant differences for TTE or length of hospital stay
	Mackie et al.[41]	2005	42	A composite clinical outcome score and CI at 48 post-operative hours in neonates undergoing CPB.	Shorter median time to negative fluid balance after aortic arch reconstruction; systolic blood pressure was higher in the T3 group.	The median clinical outcome scores were similar among both groups; CI at 48 hours was not significantly improved; HR and diastolic blood pressure were not affected by T3.
	Portman et al.[29] (TRICC trial)	2010	193	TTE in children younger than 2 years old undergoing heart surgery with CPB.	Significant interaction among age and treatment; reduced TTE in children younger than 5 months of age, with a reduction in use of inotropes and improvement in cardiac function.	Overall, TTE was similar among groups; no differences in adverse event rates, including arrhythmia; no significant differences for HR, mean arterial blood pressure over the first 24 hours
	Marwali et al.[31]	2017	208	TTE in infants and children undergoing CPB.	Age-dependent effect of T3 supplementation; shorter TTE in infants aged 5 months or younger; sepsis was more frequent with placebo.	Overall, TTE was not significantly different; LVEF was not significantly different; adverse events rates including arrhythmia were similar.
	Talwar et al.[40]	2018	100	Change in CI in infants undergoing CPB; secondary endpoints: change in IS and levels of serum inflammatory markers; clinical endpoints: TTE, ICU stay and occurrence of LCOS.	Higher CI in the T4 group. The average TISS for the first 2 days were higher in the placebo group. T4 reduced TTE, ICU and hospital stay.	Serum lactate levels were similar among the two groups with other indicators of LCOS; no statistically significant differences in morbidity indicators (sepsis, arrhythmias, re-intubation and need for CPR) and mortality.
	Zhang et al.[42]	2018	40	Perioperative serum thyroid hormones; secondary outcome measures: haemodynamic variables, TTE, duration of ICU stay, use of inotropic drugs. In children aged 3 to 12 years scheduled for elective cardiac surgery with CPB.	Inotropic requirement was significantly decreased in the T3/T4 group. Serum T3, FT3 and T4 on the first and second postoperative days, and serum FT4 on the first postoperative day were significantly higher in the trial group.	No significant differences among groups in haemodynamic variables at all observed times, TTE, and duration of ICU stay.

LVEF: left ventricular ejection fraction; SV: stroke volume; CO: cardiac output; SVR: systemic vascular resistances; T3: triiodothyronine; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CI: cardiac index; HR: heart rate; TISS: therapeutic intervention scoring system; MVO2: mixed venous oxygen saturation; ICU: intensive care unit; AXC: aortic cross-clamping; DC: dilated cardiomyopathy; TTE: time to extubation; IS: inotropic score; LCOS: low CO syndrome.

Discussion

Clinical and experimental evidence strongly support that altered thyroid homeostasis negatively influences survival in cardiac patients. This review aims at the topic of alterations in the levels of thyroid hormones characteristic of the ESS during extracorporeal circulation and the effects of T3/T4 administration in patients undergoing cardiac surgery with or without CPB and HT. In addition, the literature about thyroid function changes in patients with chronic heart failure requiring VAD placement is reviewed.

The focus on the sub-population of VAD-patients is of high interest in the current era of increasing mechanical assist device utilization. Adjunctive therapy during LVAD support may be important to improve short-term and long-term outcomes. While a good amount of literature on ESS during cardiac surgery and its influence on the cardiovascular system exists, specific pathophysiologic mechanism, implications, and randomized studies in the VAD population are lacking. Amiodarone therapy does result in hyper- or hypothyroidism dysfunction and therefore it may be justified to investigate the role of T3 in these patients who are on long-term amiodarone. The findings by Adamopoulos et al.[50] support the importance of the thyroid function and amiodarone in these VAD patients, although their study is underpowered.

Changes in thyroid function after CPB may have been widely recognized. Providers are now more aware of the benefit of T3 administration after congenital heart operations. However, administration of thyroid hormones is not currently widespread practice in the cardiac surgical field, not only HT. This review yields an update on the current literature, emphasizing on outcomes.

T3/T4 supplementation is able to ameliorate the ESS that happens in relation to the intense stress responses accompanying cardiac surgery and can be dispensed without any harmful side effects.[56] Nonetheless, despite a number of studies observing enhancement in haemodynamic function and decreased inotropic requirements, substantial advantages regarding major morbidity, mortality or postoperative arrhythmias in cardiac surgery have not been demonstrated consistently. Of the reviewed literature, only the study of Mullis-Jansson et al.[22] showed positive results with regard to prevention of postoperative atrial fibrillation. It can be speculated that the reduction in T3 levels may be a marker of a latent disorder but not the origin of the disorder. Accordingly, T3 administration may enhance haemodynamics but does not seem to improve patient outcomes to a great extent.[21] Taken together the perioperative trials, another reason for this may be that many of the trials were not designed with clinical outcomes as a primary outcome goal, and several of those that were did not have enough statistical power to detect improvements in clinical outcomes. In addition, it remains to be clarified the response of both myocardium and systemic vasculature to T3 depending on age, which may contribute also to the differences observed in outcomes among age groups.

The 2014 Consensus Statement about Paediatric Cardiac Intensive Care could not recommend the routine use of thyroid hormone replacement to normalize levels after cardiac surgery based on the evidence up to that date.[57] However, of great interest are the recent studies of Marwali et al. and the TRICC trial, which identified an age-dependent impact of T3 administration.[29,31] The study of Chowdhury et al.[46] had shown previously similar results. These data suggested a positive impact of T3 administration greater in the younger, relatively more complicated patients, but the success and security of that regimen required confirmation.

In the latest trials in children, oral thyroid hormones have been used instead of the intravenous supplementation.[40,42] This avoids the concern on intravenous administration regarding the potential for accidental overdose.[42] In addition, the availability and cost of intravenous thyroid hormones limit its widespread use.[40] Only one study investigated oral thyroid hormone supplements in adults, who underwent CABG, which was safe and resulted in less inotropic requirement and reduced length of hospital stay.[25]

Studies in the paediatric population seem encouraging, and the most recent large trials show interesting results that could support the recommendation of thyroid hormone replacement in particular sub-populations of paediatric patients.[29,31,40] The future research directions proposed by Zhang et al.[42] are to some extent accomplished by Talwar et al.[40] with regard to the need for large trials with enough statistical power for postoperative clinical outcomes and including complex cardiac surgeries. This beneficial effect observed in neonates and infants may be partially justified because the decrease in thyroid hormone levels after CPB is more profound in them as compared with adults, therefore making them more vulnerable.[40]

However, further randomized large trials should be conducted in various age strata in children investigating the timing and route of T3/T4 administration and outcomes in terms of cardiovascular performance, morbidity, mortality, and neurological development.[40,58] Clinical trials to assess benefit of T3/T4 administration during ECMO in infants and children may be desirable grounded on the overall data from human and animal research.[17]

While the accessible studies frequently suggest that thyroid hormone administration may be advantageous in the context of adult cardiac surgery, the regular utilization of thyroid hormone administration cannot yet be recommended in adults. It can be deduced the most

beneficial effect of T3/T4 administration is in those adults at higher risk of postoperative cardiac dysfunction, such as those having a preoperative LVEF < 30%. Studies in adults on this subject are more than 5 years old. In the latest review in adults, it was concluded thyroid hormone produced a transient increase in cardiac index, but it could not be determined whether it was beneficial or detrimental. Effects on new onset atrial fibrillation, inotropic requirements, duration of ICU stay and mortality were also inconclusive. These results would require more studies and larger sample sizes.[59]

Regarding the impact of thyroid hormone on cardiac performance following HT, in the latest research, there are different recommendations. The study of 2015 in humans concluded that T3/T4 therapy to the donor resulted in more transplantable hearts and lungs without damage to post-transplant graft or recipient survival.[45] However, in a study of 2017 of HT in piglets, administration of T3 to the donor conferred no beneficial effect on myocardial performance or survival following HT.[44] Despite another study of animal HT that suggested the consideration by the authors of the T3 replacement therapy.[60] Therefore, further research needs to be conducted in humans in relation to HT.

Conclusion

The routine assessment of thyroid function might be paramount in patients on extracorporeal circulation. Thyroid hormone supplementation may potentially be advantageous particularly in selected paediatric subpopulations. It is speculated that perioperative thyroid hormone supplementation can prevent the occurrence of ESS after cardiac surgery in these patients.

It is recommended the preoperative short-term administration of oral thyroid hormones (T3/T4) in children undergoing simple cardiac surgery with CPB. It is recommended oral T4 supplementation 12 hours before surgery and once daily for the remainder of the ICU stay in infants 6 months of age or younger undergoing complex congenital heart surgery with CPB. However, further evidence is needed from adequately powered studies to make firm recommendations. Further research is needed about beneficial short-term clinical outcomes with regard to cardiac function, morbi-mortality and arrhythmias, and long-term outcomes in children.

There is currently no firm evidence regarding the benefits of routine use of thyroid hormone replacement in adult cardiac patients undergoing CPB.[59] Further studies in adults at higher risk of postoperative cardiac dysfunction should be conducted. Clinical trials to assess benefit of T3/T4 administration during ECMO may be desirable. Future studies are needed to assess the beneficial effect of thyroid hormone on patients with end-stage heart failure supported by VAD.

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References

1. Klein I, Danzi S. Thyroid disease and the heart. *Curr Probl Cardiol* 2016; 41: 65–92.
2. Udovcic M, Herrera Pena R, Patham B, et al. Hypothyroidism and the heart. *Methodist Debakey Cardiovasc J* 2017; 13: 55–59.
3. Mejia Osuna P, Udovcic M, Sharma MD. Hyperthyroidism and the heart. *Methodist Debakey Cardiovasc J* 2017; 13: 60–63.
4. Klemperer JD. Thyroid hormone and cardiac surgery. *Thyroid* 2002; 12: 517–521.
5. Gomberg-Maitland M, Frishman WH. Thyroid hormone and cardiovascular disease. *Am Heart J* 1998; 135: 187–196.
6. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid* 2014; 24: 1456–1465.
7. Stewart DL, Ssemakula N, MacMillan DR, et al. Thyroid function in neonates with severe respiratory failure on extracorporeal membrane oxygenation. *Perfusion* 2001; 16: 469–475.
8. Cerillo AG, Sabatino L, Bevilacqua S, et al. Nonthyroidal illness syndrome in off-pump coronary artery bypass grafting. *Ann Thorac Surg* 2003; 75: 82–87.
9. Gabriel EA, Locali RF, Matsuoka PK, et al. On-pump coronary artery bypass graft surgery: biochemical, hormonal and cellular features. *Rev Bras Cir Cardiovasc* 2011; 26: 525–531.
10. Bremner WF, Taylor KM, Baird S, et al. Hypothalamo-pituitary-thyroid axis function during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1978; 75: 392–399.
11. Velissaris T, Tang AT, Wood PJ, et al. Thyroid function during coronary surgery with and without cardiopulmonary bypass. *Eur J Cardiothorac Surg* 2009; 36: 148–154.
12. Holland FW, Brown PS Jr, Weintraub BD, et al. Cardiopulmonary bypass and thyroid function: a 'euthyroid sick syndrome'. *Ann Thorac Surg* 1991; 52: 46–50.
13. Keçeligil HT, Kolbakir F, Adam B, et al. Thyroid hormone alterations during and after cardiopulmonary bypass. *Cardiovasc Surg* 1996; 4: 617–622.
14. Plumpton K, Haas NA. Identifying infants at risk of marked thyroid suppression post-cardiopulmonary bypass. *Intensive Care Med* 2005; 31: 581–587.

15. Talwar S, Khadgawat R, Sandeep JA, et al. Cardiopulmonary bypass and serum thyroid hormone profile in pediatric patients with congenital heart disease. *Congenit Heart Dis* 2012; 7: 433–440.
16. Cerillo AG, Storti S, Kallushi E, et al. The low triiodothyronine syndrome: a strong predictor of low cardiac output and death in patients undergoing coronary artery bypass grafting. *Ann Thorac Surg* 2014; 97: 2089–2095.
17. Files MD, Kajimoto M, O'Kelly Priddy CM, et al. Triiodothyronine facilitates weaning from extracorporeal membrane oxygenation by improved mitochondrial substrate utilization. *J Am Heart Assoc* 2014; 3: e000680.
18. Priest JR, Slee A, Olson AK, et al. Triiodothyronine supplementation and cytokines during cardiopulmonary bypass in infants and children. *J Thorac Cardiovasc Surg* 2012; 144: 938–943.
19. Leeuwen L, van Heijst AFJ, van Rosmalen J, et al. Changes in thyroid hormone concentrations during neonatal extracorporeal membrane oxygenation. *J Perinatol* 2017; 37: 906–910.
20. Leeuwen L, van Heijst AF, Vijfhuize S, et al. Nationwide evaluation of congenital hypothyroidism screening during neonatal extracorporeal membrane oxygenation. *Neonatology* 2016; 111: 93–99.
21. Reichert MG, Verzino KC. Triiodothyronine supplementation in patients undergoing cardiopulmonary bypass. *Pharmacotherapy* 2001; 21: 1368–1374.
22. Mullis-Jansson SL, Argenziano M, Corwin S, et al. A randomized double-blind study of the effect of triiodothyronine on cardiac function and morbidity after coronary bypass surgery. *J Thorac Cardiovasc Surg* 1999; 117: 1128–1134.
23. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary-artery bypass surgery. *N Engl J Med* 1995; 333: 1522–1527.
24. Choi YS, Shim JK, Song JW, et al. Efficacy of perioperative oral triiodothyronine replacement therapy in patients undergoing off-pump coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 2013; 27: 1218–1223.
25. Sirlak M, Yazicioglu L, Inan MB, et al. Oral thyroid hormone pretreatment in left ventricular dysfunction. *Eur J Cardiothorac Surg* 2004; 26: 720–725.
26. Carrel T, Eckstein F, Englberger L, et al. Thyronin treatment in adult and pediatric heart surgery: clinical experience and review of the literature. *Eur J Heart Fail* 2002; 4: 577–582.
27. Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2008; 93: 1351–1358.
28. Bettendorf M, Schmidt KG, Jurgen GH, et al. Triiodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study. *Lancet* 2000; 356: P529–P534.
29. Portman MA, Slee A, Olson AK, et al. Triiodothyronine supplementation in infants and children undergoing cardiopulmonary bypass (TRICC) a multicenter placebo-controlled randomized trial: age analysis. *Circulation* 2010; 122: S224–S233.
30. Portman MA, Fearneyhough C, Ning XH, et al. Triiodothyronine repletion in infants during cardiopulmonary bypass for congenital heart disease. *J Thorac Cardiovasc Surg* 2000; 120: 604–608.
31. Marwali EM, Boom CE, Budiwardhana N, et al. Oral triiodothyronine for infants and children undergoing cardiopulmonary bypass. *Ann Thorac Surg* 2017; 104: 688–695.
32. Kajimoto M, Priddy CM, Ledee DR, et al. Effects of continuous triiodothyronine infusion on the tricarboxylic acid cycle in the normal immature swine heart under extracorporeal membrane oxygenation in vivo. *Am J Physiol Heart Circ Physiol* 2014; 306: H1164–H1170.
33. Güden M, Akpinar B, Sagğbaş E, et al. Effects of intravenous triiodothyronine during coronary artery bypass surgery. *Asian Cardiovasc Thorac Ann* 2002; 10: 219–222.
34. Bennett-Guerrero E, Jimenez JL, White WD, et al. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo-controlled trial. Duke T3 study group. *JAMA* 1996; 275: 687–692.
35. Kadletz M, Mullen PG, Ding M, et al. Effect of triiodothyronine on postischemic myocardial function in the isolated heart. *Ann Thorac Surg* 1994; 57: 657–662.
36. Dyke CM, Ding M, Abd-Elfattah AS, et al. Effects of triiodothyronine supplementation after myocardial ischemia. *Ann Thorac Surg* 1993; 56: 215–222.
37. DiPierro FV, Bavaria JE, Lankford EB, et al. Triiodothyronine optimizes sheep ventriculoarterial coupling for work efficiency. *Ann Thorac Surg* 1996; 62: 662–669.
38. Novitzky D, Cooper DK, Barton CI, et al. Triiodothyronine as an inotropic agent after open heart surgery. *J Thorac Cardiovasc Surg* 1989; 98(5 Pt 2): 972–977; discussion 977–978.
39. Ranasinghe AM, Quinn DW, Pagano D, et al. Glucose-insulin-potassium and tri-iodothyronine individually improve hemodynamic performance and are associated with reduced troponin I release after on-pump coronary artery bypass grafting. *Circulation* 2006; 114(1 Suppl.): I245–I250.
40. Talwar S, Bhoje A, Khadagawat R, et al. Oral thyroxin supplementation in infants undergoing cardiac surgery: a double-blind placebo-controlled randomized clinical trial. *J Thorac Cardiovasc Surg* 2018; 156: 1209–1217.e3.
41. Mackie AS, Booth KL, Newburger JW, et al. A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. *J Thorac Cardiovasc Surg* 2005; 130: 810–816.
42. Zhang JQ, Yang QY, Xue FS, et al. Preoperative oral thyroid hormones to prevent euthyroid sick syndrome and attenuate myocardial ischemia-reperfusion injury after cardiac surgery with cardiopulmonary bypass in children: a randomized, double-blind, placebo-controlled trial. *Medicine* 2018; 97: e12100.
43. Klemperer JD, Ojamaa K, Klein I. Thyroid hormone therapy in cardiovascular disease. *Prog Cardiovasc Dis* 1996; 38: 329–336.
44. Kumar TKS, Mathis C, Sathanandam S, et al. Effect of thyroid hormone on cardiac function following

orthotopic heart transplantation in piglets. *Pediatr Transplant* 2017; 21. DOI: 10.1111/petr.13002.
45. Novitzky D, Mi Z, Collins JF, et al. Increased procurement of thoracic donor organs after thyroid hormone therapy. *Semin Thorac Cardiovasc Surg* 2015; 27: 123–132.
46. Chowdhury D, Ojamaa K, Parnell VA, et al. A prospective randomized clinical study of thyroid hormone treatment after operations for complex congenital heart disease. *J Thorac Cardiovasc Surg* 2001; 122: 1023–1025.
47. Ito K, Kagaya Y, Shimokawa H. Thyroid hormone and chronically unloaded hearts. *Vascul Pharmacol* 2010; 52(3–4): 138–141.
48. Noirhomme P, Jacquet L, Underwood M, et al. The effect of chronic mechanical circulatory support on neuroendocrine activation in patients with end-stage heart failure. *Eur J Cardiothorac Surg* 1999; 16: 63–67.
49. Wieselthaler GM, Riedl M, Schima H, et al. Endocrine function is not impaired in patients with a continuous MicroMed-DeBakey axial flow pump. *J Thorac Cardiovasc Surg* 2007; 133: 2–6.
50. Adamopoulos S, Gouziouta A, Mantzouratou P, et al. Thyroid hormone signalling is altered in response to physical training in patients with end-stage heart failure and mechanical assist devices: potential physiological consequences? *Interact Cardiovasc Thorac Surg* 2013; 17: 664–668.
51. Davies PH, Franklyn JA. The effects of drugs on tests of thyroid function. *Eur J Clin Pharmacol* 1991; 40: 439–451.
52. Newman CM, Price A, Davies DW, et al. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998; 79: 121–127.
53. Chin C, Feindel C, Cheng D. Duration of preoperative amiodarone treatment may be associated with postoperative hospital mortality in patients undergoing heart transplantation. *J Cardiothorac Vasc Anesth* 1999; 13: 562–566.
54. Rahman A, Akbulut H, Bayar MK, et al. The effects of intraoperative amiodarone loading on the systemic inflammatory response syndrome induced by cardiopulmonary bypass. *Anadolu Kardiyol Derg* 2009; 9: 318–324.
55. Rajapreyar I, Acharya D, Tallaj J, Hornbuckle L, et al. Left ventricular assist device thrombosis-amiodarone-induced hyperthyroidism: causal link? *ASAIO J* 2019; 65: e18–e20.
56. Ranasinghe AM, Bonser RS. Thyroid hormone in cardiac surgery. *Vascul Pharmacol* 2010; 52: 131–137.
57. Soto-Rivera CL, Agus MS, Sawyer JE, et al. Pediatric Cardiac Intensive Care Society 2014 consensus statement: pharmacotherapies in cardiac critical care hormone replacement therapy. *Pediatr Crit Care Med* 2016; 17(3 Suppl. 1): S59–S68.
58. Dimmick S, Badawi N, Randell T. Thyroid hormone supplementation for the prevention of morbidity and mortality in infants undergoing cardiac surgery. *Cochrane Database Syst Rev* 2004; 3: CD004220.
59. Kaptein EM, Sanchez A, Beale E, et al. Thyroid hormone therapy for postoperative nonthyroidal illnesses: a systematic review and synthesis. *J Clin Endocrinol Metab* 2010; 95: 4526–4534.
60. Iwase H, Ekser B, Hara H, et al. Thyroid hormone: relevance to xenotransplantation. *Xenotransplantation* 2016; 23: 293–299.

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The Great Ormond Street Hospital immunoadsorption method for ABO-incompatible heart transplantation: a practical technique

Richard Issitt,[1,2] Richard Crook,[1] Michael Shaw[1] and Alex Robertson[1]

Abstract

Traditionally, ABO-incompatible heart transplantation was accomplished using a plasma exchange technique to remove recipient plasma containing donor-incompatible anti-A/B isohaemagglutinins. However, this technique exposed patients to large volumes of allogeneic blood and blood products (up to three times the patient's circulating volume). In 2018, we published the first reported case of an ABO-incompatible heart transplant using an intraoperative immunoadsorption technique which minimises the exposure to blood products by specifically targeting anti-A/B isohaemagglutinins. We have subsequently used this technique in all children undergoing ABO-incompatible heart transplantation and become convinced of its efficacy in this population while observing no adverse effects. This article outlines the practical details required to perform the technique in order to avoid hyperacute rejection.

Keywords

immunoadsorption; heart transplantation; isohaemagglutinins; cardiopulmonary bypass

Introduction

The concept and first practical method of ABO-incompatible (ABO-i) heart transplantation was introduced by West et al.[1] in 2001. Using a plasma exchange technique, undertaken before the onset of cardiopulmonary bypass (CPB) (which utilises blood cells matched to the recipient, and plasma and platelets matched to the donor), the immaturity of the recipient's immune system was exploited to enable the crossing of the ABO blood group barrier.[2,3] This technique, however, entailed a period of potential haemodynamic instability where mechanical support could not be initiated without sacrificing the efficacy of the plasma exchange process.[3] Initial work suggested that the technique was limited to the first 12-14 months of life as after this isohaemagglutinin titres were higher and risked acute rejection. Further work by the West group and others saw this time frame extended well beyond this point, with the oldest reported successful procedure carried out in a 5-year-old girl in Sweden.[3–5] While highly successful, showing comparable outcome data to ABO-compatible heart transplantation,[6] the procedure exposed patients to vast quantities of allogeneic blood and blood products (at least three times the patient's circulating volume), increasing the risk of transfusion-related morbidity.[3,7] This is especially prevalent in patients >10 kg where the required volumes for plasma exchange can exceed 3 L, thereby substantially increasing the number of donor exposures. To address this, we sought to target the anti-A/B isohaemagglutinins directly, through the process of immunoadsorption (IA), rather than indirectly as a consequence of displacing the patient's blood volume. We reasoned this would have a number of benefits. First, the process could be undertaken during the operation, as opposed to extending the period in theatre which is necessary for the plasma exchange process, thus avoiding the period of potential instability. Second, by avoiding the massive

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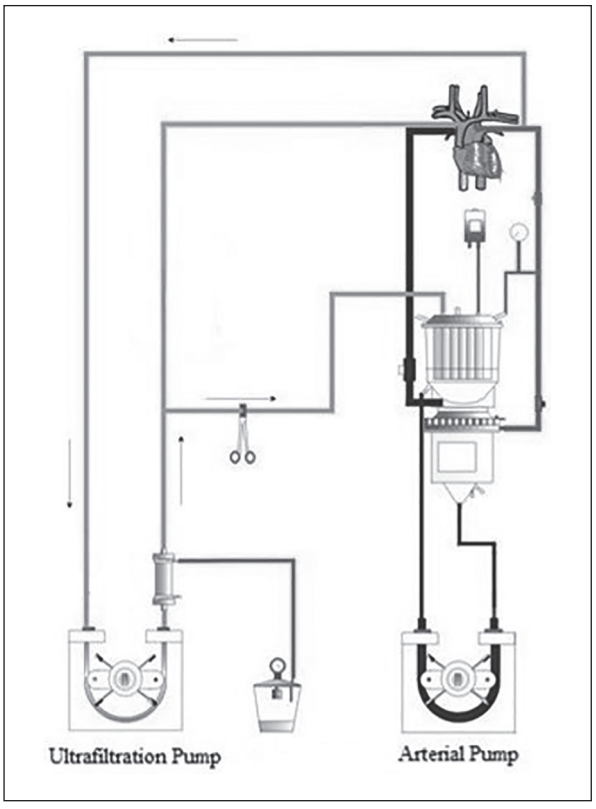

Figure 1. Standard CPB setup. Blood for filtration is taken via the ultrafiltration pump from the arterial limb of the bypass circuit. The filtrate is removed under vacuum and the haemoconcentrated blood is returned to systemic circulation via the venous reservoir or back to the right atrium via a wye (Y) connector for performing modified ultrafiltration.

transfusion requirements, disruption to homeostasis is avoided, and the physiological insult and subsequent morbidity are minimised. This approach resulted in accomplishing ABO-i heart transplants with a substantial reduction in blood and blood product transfusion while also avoiding hyperacute rejection.[8]

The purpose of this communication is to describe the technique in more practical detail for the benefit of other centres wishing to utilise this process.

Methods

Standard setup

Our standard CPB setup is using a S5 heart-lung bypass machine (Stockert; LivaNova, Munich, Germany), with a mast-mounted single arterial pump (150 mm diameter) and two mast-mounted double-headed pumps (85 mm diameter). These are used for extra-cardiac suction and intra-cardiac venting and haemofiltration. There is also a base-mounted double-headed pump (85 mm diameter) for cardioplegia delivery. As our haemofiltration line arises from the arterial limb of the CPB circuit (Figure 1), the haemofiltration pump is slaved to the main arterial pump to prevent cavitation during modified ultrafiltration. For a typical patient of 5 kg undergoing ABO-i heart transplantation, the CPB circuit consists of a tubing set with a 3/16″ arterial line and 1/4″ venous line (LivaNova) with an oxygenator with hardshell venous reservoir (CAPIOX® FX05; Terumo, Leuven, Belgium). The haemofiltration circuit described above takes blood from the arterial line and returns it, via a wye (Y) connector, either to the venous reservoir or, via a 1/8″ line, to the right atrium for modified ultrafiltration as previously described.[9]

ABO-i IA modified circuit

To facilitate anti-A/B isohaemagglutinin removal, plasma must be separated from the circulating volume. To the above circuit, a plasma separator (Asahi Kasei PS-03; LINC Medical Systems Ltd, Leicester, UK) is placed in parallel to the haemofilter (HF-06; LivaNova) using a positive screw locking (POS lock)–ended wye connector to the haemofiltration line (Figure 2). Distal to both the plasma separator and haemofilter, a second POS lock–ended wye connector is used to recombine the two streams. This, in turn, is then further split via a wye for return to the venous reservoir or via a 1/8″ line to the right atrium as described above.

The rate of effluent (plasma) flow must be controlled, and so an additional roller pump (described here as the IA pump; 150 mm diameter) is attached to the mast with the haemofiltration pump. This takes the separated plasma to the anti-A/B IA column (Glycosorb®-ABO Anti-A/B Specific Column; Glycorex Transplantation AB, Lund, Sweden), which removes both anti-A and anti-B isohaemagglutinins. The post–plasma separator blood and post–IA column plasma are then reconstituted into a single line returning to the systemic circulation via the venous reservoir. In order to prevent a mismatch in flow through the plasma separator, and effluent plasma flow to the IA column, the IA pump is slaved to the haemofiltration pump and locked to prevent a faster flow rate in the former.

Priming

Following priming of the main systemic CPB circuit, flow is then initiated through the haemofilter, and once de-aired is clamped off from the circuit. Flow is then passed through the plasma separator at an initial rate of 50 mL/min and increased to 200 mL/min over 5 min. This is the maximum recommended rate for the plasma separator described here. Once the plasma separator is de-aired, the IA pump is started and increased to a

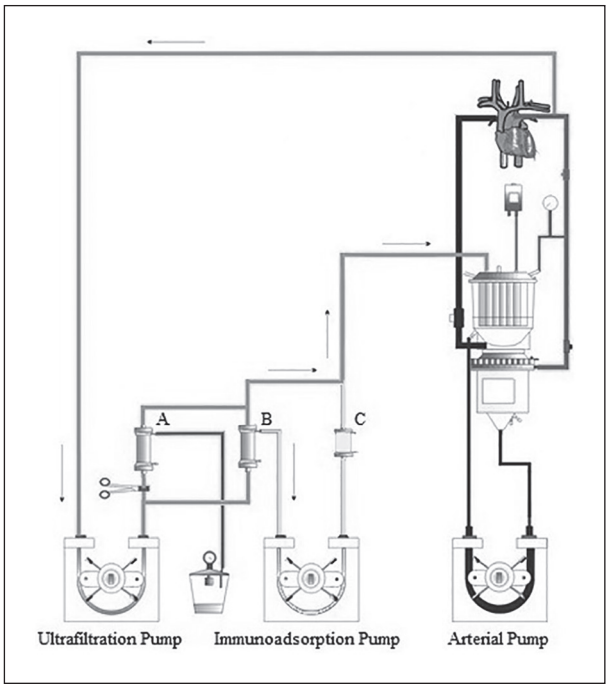

Figure 2. CPB circuit with integrated immunoadsorption column. Whole blood is pumped, using the ultrafiltration pump, from the arterial limb of the bypass circuit via the plasma separator (B). The haemofilter (A) is clamped from the circuit at this stage, having been used for pre-bypass ultrafiltration and later for conventional and modified ultrafiltration. The separated plasma is then pumped through the anti-A/B immunoadsorption column (C) via the immunoadsorption pump. The haemic content from the plasma separator outlet is reconstituted with the anti-A/B depleted plasma and returned to the circulation via the venous reservoir.

maximum flow rate of 40 mL/min over 5 min. This is the maximum recommended rate for the anti-A/B IA column described here. Once fully primed, both circuits can be clamped off ready for initiation of CPB. The manufacturer stipulates that air must not be allowed to enter the IA column during circuit priming. Therefore, the inflow to the column can either be detached as the line fills with fluid from the plasma separator or a three-way stopcock may be placed at the inflow to the column to remove air from the line until it is filled with fluid.

CPB management

Once CPB has been established, the flows through the plasma separator and subsequently the IA column can be increased to the rates outlined above. This can be left to run for the required duration of treatment before reperfusion of the donor organ occurs (discussed in the following section) and for the remainder of the CPB run following X-clamp removal (though the target titre of 1:2 or better should be achieved prior to reperfusion). Due to the shunting of arterial flow required for this technique, the flow rate of the main arterial pump should be increased to compensate. During the setup of the circuit, it is vital to account for this when calculating cardiac index as this will influence the selection of arterial pump boot size necessary.

A word of caution should also be noted should haemofiltration be required during the IA process, especially if vacuum is applied to the haemofiltration effluent line; this can cause preferential blood flow through the haemofilter at the expense of the plasma separator. This results in a reduction of separated plasma for the IA pump, despite a constant flow being maintained on the effluent of the plasma separator. To reduce the possibility of this occurring, a flow probe should be placed on the blood outlet of the plasma separator and the haemofiltration pump flow increased to compensate to ensure sufficient blood flow through it and thus prevent rupturing of the plasma separator fibres that may occur otherwise.

Duration of IA treatment

We have previously covered the issue of patient suitability and selection, so will not discuss here.[8] The recommended treatment time (the length of IA prior to reperfusion of the donor organ) is calculated as follows

$$\text{Minimum treatment time (min)} = \frac{\left(PaV(\text{mL}) + TPV(\text{mL})\right) * \left(\frac{\left(100 - Hct\right)}{100}\right)}{40\ \text{mL/min}} * nPV$$

where *PaV* is the patient's circulating volume, *TPV* is the total prime volume, *Hct* is the patient's haematocrit and *nPV* is the number of plasma volumes for treatment

Based on our previous experience, the recommended number of PV that passes through the IA column should equal the number of titre reductions required to ensure a maximum final concentration of 1:2. For instance, a patient with a starting titre of 1:32 requires a minimum of four PV passes through the IA column before reperfusion of the donor organ occurs. Therefore, the calculated rate multiplied by the number of PV passes required equals the minimum duration of IA treatment. An example is a 5-kg child with a circulating volume of 425 mL, 30% haematocrit and titre of 1:32 undergoing this process with a 450-mL total prime volume

$$\text{Minimum treatment time} = \frac{425 + 450 * \left(\frac{\left(100 - 30\right)}{100}\right)}{40\ \text{mL/min}} * 4$$

$$\text{Minimum treatment time} = \frac{875\ \text{mL} * 0.7}{40\ \text{mL/min}} * 4$$

$$\text{Minimum treatment time} = 62\ \text{min}$$

While in practice, due to the dilutional effects of the CPB volume, the isohaemagglutinin titre drops following initiation of CPB, we do not adjust the calculations to reflect this, preferring instead to accept the overestimation of the process.

Conclusion

The process of ABO-i heart transplantation has been utilised for over 20 years with excellent outcomes comparable to ABO-compatible transplantation.[10] However, the initially described methodology of plasma exchange transfusion puts patients at increased risk of transfusion-related morbidity due to the significant volumes of blood and blood products required.[7] The modification to the methodology described here has the potential to drastically reduce this impact. In the first reported case using this technique, the patient received two units (520 mL) of packed red blood cells and one unit (200 mL) of plasma. Had they undergone the plasma exchange method, the patient would have received eight units of packed red cells (~2,000 mL) and 10 units (2,000 mL) of plasma in a 1:1 ratio, significantly increasing donor exposure and subsequent risk of transfusion-related morbidity.[8]

We believe that this technique has several positive implications for paediatric heart transplantation. First, we have previously shown that the process is predictable and efficient, allowing for planning of time needed for isohaemagglutinin removal before donor organ reperfusion.[8] Second, patients have less blood product exposure and are not subject to the hemodynamic instability from fluid shifts associated with the plasma exchange technique.[3,8] Finally, and perhaps most significantly, we believe that this technique has the potential to expand the application of ABO-i heart transplantation to larger children and those recipients with higher anti-A/B isohaemagglutinin titres than traditionally treated, although more research is needed to explore this. Given the increasing demand for donor hearts within a relatively constant or even falling level of donor organ availability, we hope this method may assist in maximising the effective donor pool for our patients.[11]

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References

1. West LJ, Pollock-Barziv SM, Dipchand AI, et al. ABO-incompatible heart transplantation in infants. *N Engl J Med* 2001; 344: 793–800.
2. Foreman C, Gruenwald C, West L. ABO-incompatible heart transplantation: a perfusion strategy. *Perfusion* 2004; 19: 69–72.
3. Issitt RW, Crook RM, Cross NT, et al. Incompatible ABO-plasma exchange and its impact on patient selection in paediatric cardiac transplantation. *Perfusion* 2012; 27: 480–485.
4. West LJ. ABO-incompatible hearts for infant transplantation. *Curr Opin Organ Transplant* 2011; 16: 548–554.
5. Bucin D, Johansson S, Malm T, et al. Heart transplantation across the antibodies against HLA and ABO. *Transp Int* 2006; 19: 239–244.
6. Saczkowski R, Dacey C, Bernier P-L. Does ABO-incompatible and ABO-compatible neonatal heart transplant have equivalent survival? *Interact Cardiovasc Thorac Surg* 2010; 10: 1026–1033.
7. Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007; 116: 2544–2552.
8. Robertson A, Issitt R, Crook R, et al. A novel method for ABO-incompatible heart transplantation. *J Heart Lung Transplant* 2018; 37: 451–457.
9. Naik SK, Knight A, Elliott M. A prospective randomized study of a modified technique of ultrafiltration during pediatric open-heart surgery. *Circulation* 1991; 84: III422–III431.
10. Patel ND, Weiss ES, Scheel J, et al. ABO-incompatible heart transplantation in infants: analysis of the united network for organ sharing database. *J Heart Lung Transplant* 2008; 27: 1085–1089.
11. Simpson KE, Canter C. Can we push the boundaries of ABO-incompatible pediatric heart transplantation? *J Heart Lung Transplant* 2018; 37: 433–434.

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Challenges and possibilities of developing cardiac surgery in a peripheral hospital of low- and middle-income countries

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Abstract

Objective: Over a million cardiac surgeries are performed every year around the globe. However, approximately 93% of world population living in low- and middle-income countries have no access to cardiac surgery. The incidence of rheumatic and congenital heart disease is high in Nepal, while only 2,500-3,000 cardiac surgeries are performed annually. The aim of our study is to analyze challenges and opportunities of establishing a cardiac surgery program in a peripheral hospital of Nepal.

Methods: We analyzed our effort to establish a cardiac surgery program in a peripheral hospital in Nepal.

Results: Out of 2,659 consulted and diagnosed patients, we performed 85 open-heart surgeries in 4 years. Mean age of patients was 38.35 ± 14.13 years. The majority of patients were male (62.4% of patients) with 65.9% suffering from rheumatic heart disease. Average intensive care unit stay and hospital stay were 2.32 ± 1.1 and 8.29 ± 2.75 days, respectively. No in-hospital mortality was observed.

Conclusion: We conclude that developing cardiac surgical care in a peripheral hospital of a developing country is feasible with support from government, foreign colleagues, local teams, and non-governmental organizations. The availability of a regular cardiac surgery service in the periphery of the country makes such services more accessible for the patients and helps in reducing the long waiting lists and unmanageable workload in the established cardiac centers in the capital city.

Keywords

cardiac surgery; challenges; low- and middle-income countries; developing countries; possibilities

Introduction

Nearly one century ago, the heart was considered a sacrosanct organ. Ambroise Paré wrote: "The Heart is the chief mansion of the Soule, the organ of vital faculty, the beginning of life, the fountain of the vital spirits, and so consequently the continual nourisher of the vital heat, the first living and last dying."[1] Aristotle once claimed that "the heart alone of all viscera cannot withstand serious injury."[1] Moreover, Billroth warned that "a surgeon who tries to suture a heart wound deserves to lose esteem of his colleague." In other words, cardiac surgery was long considered dangerous territory, a line not to be traversed. And yet, in 1896, Ludwig Rehn of Frankfurt crossed that line, performing the first successful repair of a cardiac stab wound. However, it was only during the Second World War that cardiac surgery really took off. In 1944, Alfred Blalock successfully performed the innovative Blalock–Taussig–Thomas shunt on a patient with Tetralogy of Fallot at the Johns Hopkins Hospital, igniting enthusiasm and hope among surgeons to attempt open-heart surgery. After John Gibbon's invention of the cardiopulmonary bypass machine in 1953, open-heart surgery spread from the few to many.

Approximately one million cardiac surgeries are performed around the globe every year, in roughly 4,000

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cardiac surgery centers.[2] Most of the centers are present in high-income countries, with a striking maldistribution of access relative to low- and middle-income countries (LMICs). Based on recent reports, it can be estimated that six billion people (93%) in LMICs have limited to no access to cardiac surgery.[3,4] In these countries, the burden of coronary artery disease is increasing, and the burden of congenital heart disease (CHD) and rheumatic heart disease (RHD) persists. An estimated 85-90% of the world's children are born in places without ready availability of cardiac surgery, such that there are about one million children worldwide, including Nepal, that are born with heart problems awaiting surgery. As a result, worldwide, over 100,000 infants die due to treatable CHD every year.[5–8]

Cardiac surgery in Nepal started in the early 1990s. However, its development and accessibility to the general population had been limited only to the capital city, Kathmandu, which is a general trend in most LMICs. Establishing and developing new cardiac surgery centers in the periphery has become of paramount importance due to the vast need for cardiac care in countries around the world, especially those with larger population sizes. However, in Nepal, little governmental efforts exist to do so.

The aim of our study is to analyze the challenges and opportunities of establishing a cardiac surgery program in a peripheral hospital in the low-income country of Nepal.

Materials and methods

This is a retrospective review study to evaluate the establishment of a new cardiac surgery program in a tertiary care private medical college, College of Medical Sciences, Teaching Hospital, Bharatpur, in a peripheral city in Nepal. The local institutional review board approved this study. Nepal is a low-income country (gross domestic product per capita US$3,090) in South Asia with a population of 28.1 million people, of which 30% are children. In 2017, the life expectancy at birth was 70 years, and ischemic heart disease had become the leading cause of mortality in the country, with noncommunicable diseases being responsible for over half of all deaths every year.

The cardiac surgery department was established by a local cardiac team, which performed open-heart surgery for the first time in a peripheral hospital in Nepal in December 2014, performing an atrial septal defect closure. Between June 2014 and June 2018, 2,659 patients requiring cardiac surgical care were consulted. Most of the patients were referred from cardiologists with surgical indication after thorough clinical evaluation, electrocardiogram, and echocardiography, and, where necessary, coronary angiography was performed. Other patients were identified during regular screening camps in the far villages and schools. Patients with complex CHDs (Risk Adjustment for Congenital Heart Surgery (RACHS) score 4 and above) were referred to the specialized centers dealing with complex CHD in Kathmandu, Nepal or abroad. Necessary equipment and instruments for the cardiac surgery were procured by the hospital in advance, but consumables and cardiac drugs were arranged for each case a day before the surgery. Blood bank facility is available within the hospital territory.

Results

Out of 2,659 consulted and diagnosed patients, we have performed 85 open-heart surgeries in the first four-year period. Patients' demographic data are presented in Table 1. The majority of patients were male (n = 53, 62.4%). The average age of the patients was 38.3 ± 14.1 years. Most of the patients presented with RHD (n = 56, 65.9%), while only seven (8.2%) patients presented with degenerative valvular heart disease. We performed mitral valve replacement (n = 35, 41.2%), aortic valve replacement (n = 13, 15.3%), double valve replacement (n = 9, 10.6%), mitral valve repair (n = 6, 7.1%), and tricuspid valve repair (n = 30, 35.3%). St. Jude mechanical valve prostheses (St. Jude Medical, Saint Paul, Minnesota, USA) were used during the valve replacements. Mitral valve repair was done by triangular or quadrangular resection of the mitral leaflet at the prolapse site and mitral annuloplasty using semi-rigid rings (Edwards Lifesciences, Irvine, CA, USA), where needed. Only 10 (11.8%) patients presented with CHDs. Out of these, six (7.1%) patients were operated for atrial septal defects, two (2.3%) for ventricular septal defects, one (1.2%) for an intracardiac repair for Tetralogy of Fallot, and one (1.2%) with patent ductus arteriosus. In total, 12 (14.1%) patients underwent coronary artery bypass grafting (CABG). All of the surgeries were performed under general anesthesia according to the standard protocol used in cardiac surgery and all of the CABGs were performed using cardiopulmonary bypass machine. In our cohort, the mean Euroscore II was 5.3 ± 4.9% (range of 1.3-23.5), mean extubation time was 7.5 ± 2.3 hours (range of 3-16 hours), and average intensive care unit (ICU) stay and hospital stay were 2.3 ± 1.1 (range of 1-11 days) and 8.2 ± 2.7 (range of 5-24 days) days, respectively. Our ICU was managed by cardiac surgeons in collaboration with the anesthesiologists. On the day of surgery, the operating surgeon remained in the ICU until the patients were stable and extubated. Two nursing staffs per patient were allocated to take care of the patients. Only one patient with severe mitral stenosis and severe tricuspid regurgitation, which was operated 1 day before great earthquake of Nepal, had a significantly prolonged ICU stay (11 days). After 2 weeks of discharge from the hospital, he had developed sinus bradycardia

Table 1. Demographic variables of the patients.

S. No.	Variables	Number (%)	
1	Total operated patients	85 (100%)	
2	Male	53 (62.4%)	
3	Female	32 (37.6%)	
4	Rheumatic heart disease	56 (65.9%)	
	Mitral valve replacement	35 (41.2%)	
	Aortic valve replacement	13 (15.3%)	
	Double valve replacement	9 (10.6%)	
	Mitral valve repair	6 (7.1%)	
	Tricuspid valve repair	30 (35.3%)	
5	Degenerative valvular heart disease	7 (8.2%)	
6	Congenital heart disease	10 (11.8%)	
	Atrial septal defect	6 (7.1%)	
	Ventricular septal defect	2 (2.3%)	
	Tetralogy of Fallot	1 (1.2%)	
	Persistent ductus arteriosus	1 (1.2%)	
7	Coronary artery bypass grafting	12 (14.1%)	
8	Euroscore II	5.3 ± 4.9%	Range of 1.3-23.5
9	Mean extubation time (hours)	7.5 ± 2.3	Range of 3-16 hours
10	Intensive care unit stay	2.3 ± 1.1	Range of 1-11 days
11	Hospital stay	8.2 ± 2.7	Range of 5-24 days
12	30-day mortality	0	

and syncope. A temporary pacemaker (TPI) was inserted and treated medically, but the patient could not be weaned off TPI. Consequently, a permanent pacemaker was implanted. No in-hospital and 30-day mortality was observed. Two patients (one from India and one from rural Nepal) were not present for physical follow-up. However, both patients were contacted by phone and they were symptomatically doing well. All other operated patients are under regular in-person follow-up. Valve replacement patients were followed every month in international normalized ratio (INR) clinics and dose of oral anticoagulants were adjusted accordingly.

Discussion

Cardiovascular diseases (CVDs) are the leading cause of death around the world. According to World Health Organization estimates, every year about 17.9 million people die of CVD, equaling 31% of all global deaths.[9] Recently, the burden of CVD has been increasing rapidly in LMICs amid the epidemiological transition, whereby LMICs are increasingly faced with non-communicable disease burdens. Today, about 80% of all CVD deaths occur in LMICs. Disturbingly, despite being a preventable disease and nearly eradicated in high-income countries, an estimated 33 million people still suffer from RHD worldwide.[10] In LMICs, only 11% of patients undergo much-needed operations, underlining the fact that RHD is still a disease of poverty and social injustice. Globally, RHD remains the leading cause of heart failure in children, adolescents, and young adults, accounting for over 200,000 deaths annually.[11]

It is estimated that more than 75,000 patients are suffering from RHD in Nepal.[12] About 10-15% of these patients need surgical treatment sooner or later, yet 2,000 patients die every year without getting proper treatment. Thousands of young men and women become disabled due to a disease which could be prevented or treated with good prognosis if rheumatic fever would have been diagnosed on time.[13] As expected, the majority of patients operated in our center were burdened with RHD leading to substantial valvular heart disease.

Furthermore, due to changes in lifestyle, obesity, food habits, and increased tobacco use, the burden of ischemic heart disease is rising rapidly in Nepal. It has been shown that the prevalence of coronary heart disease in Nepal is about 5.7-15%.[14] Most of the acute coronary artery cases cannot reach a hospital in time, either dying at home or on the way to a hospital. In our series, 14.1% patients underwent CABG, which could be increased by providing easily available transportation from the rural areas and financial support from the government's scheme, non-governmental organizations, and philanthropists.

CHD remains another vast area, which has not been adequately addressed in Nepal to date. CHD constituted about six in 100 hospital admissions in major hospitals of Nepal.[15] Unfortunately, a lack of trained manpower, antenatal diagnoses, and poor access to cardiac care

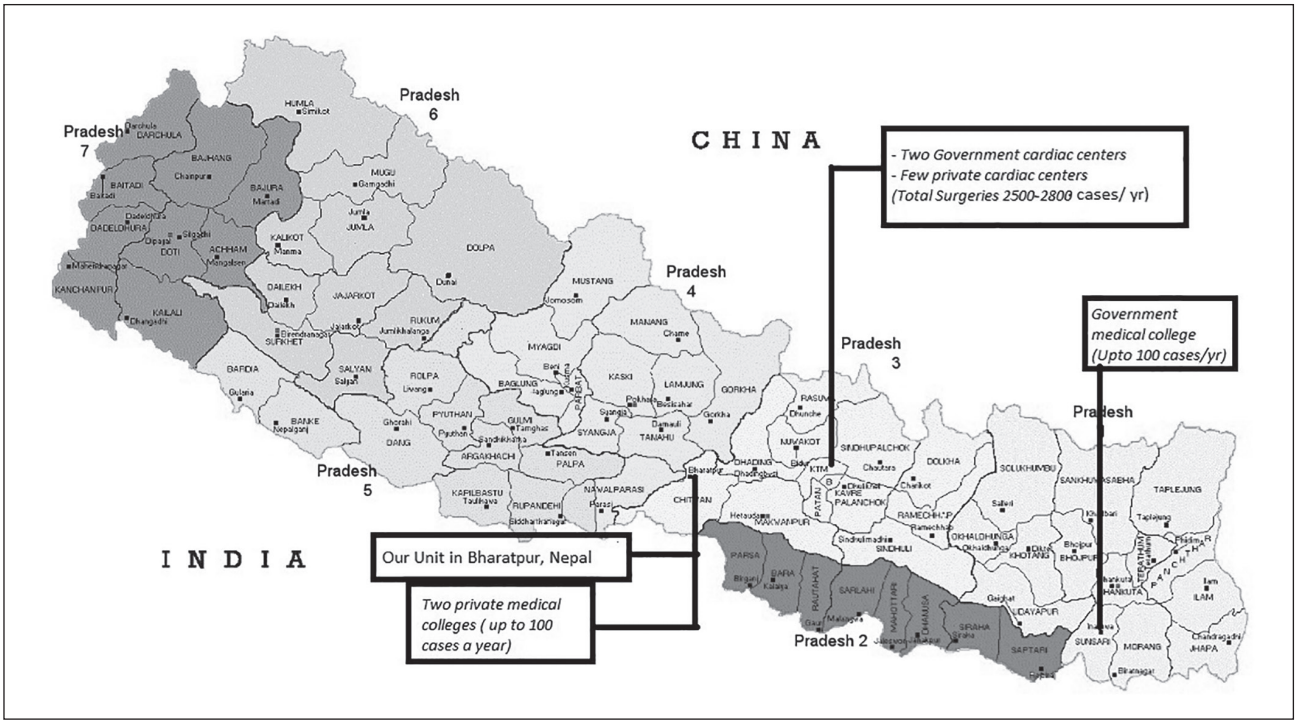

Figure 1. Map of Nepal, showing centers with cardiac surgery facilities.

during the early neonatal period causes premature death of the majority of babies born with CHD in Nepal each year. Among those who survive, most of them do not reach their fifth birthday. Fortunately, treatment of CHD cases below 14 years of age in government hospitals of Nepal is free of cost. However, due to several reasons, these schemes are not extended to peripheral private hospitals. Nonetheless, 12% of our operated patients presented with CHD.

Most of the cardiac surgeries are being performed in high-income countries, where the majority of cardiac centers are present. As reported by Vervoort et al.,[16] the disparities in the availability and distribution of cardiac surgeons is a major factor in rendering quality cardiac surgical care to patients in LMICs. There are about 22 cardiac surgeons for a population of 28 million in Nepal, which is one surgeon per 1.4 million populations, in comparison to 11.12 surgeons per million populations in North America. There are two government-run hospitals in Kathmandu regularly performing cardiac surgery and few private hospitals performing it rarely. In the periphery of the country, since the establishment of our program, two additional private medical colleges in Chitwan, the central part of Nepal, and one hospital in Dharan, the Eastern part of the country, have started performing cardiac surgery at low volumes (Figure 1). As a result, today, there is approximately one cardiac center per five million populations in Nepal. This maldistribution has a significant impact on the number of operations performed. In Nepal, approximately 2,500-3,000 cardiac operations have been performed yearly. Furthermore, there are not enough resources and manpower to cope with the huge patient flow in Kathmandu. In fact, the existing government cardiac centers are not in a condition to cope with this vast problem. What they are doing is only the tip of an iceberg, as there is a huge backlog of patients to be operated. Many patients do not survive until it is their turn for surgery and die at home or become inoperable due to progression of the disease. As such, there is an urgent need of well-running cardiac centers in the peripheral hospitals of Nepal.

As a newly established department, we could perform only 85 open-heart surgeries in 4 years. This, according to international standards, is a very small number. Reasons for this are financial constraints of patients, a lack of information among patients about availability of the facility in the peripheral hospitals, an unwillingness of patients to be operated in the periphery, less referral from local physicians, competition of established centers in the capital city, and lack of a government scheme for poor patients in peripheral centers. While the world is shifting to minimally invasive surgery, robotic surgery, heart transplantation, and artificial hearts, LMICs are still struggling to provide basic cardiac surgical services to their patients. The fact that modern cardiac surgery is not available to people in Nepal is indeed not a great surprise due to the costs and infrastructure required. For the most part, the

minorities that can afford an operation in private hospitals or by traveling abroad have no problems. There are poor patients, however, who are left behind and suffer more. Consequently, there is an imperative requirement of cardiac surgical units in the peripheral hospitals of Nepal. But, there are many obstacles to be tackled. These obstacles fall into common categories: financial problems, political problems at both the national and local (institutional) levels, cultural differences such as organizational skills, lifestyles, and priorities,[17] and the proverbial "brain drain" not only to areas outside the country but also within it.[18] However, there are two cardiothoracic and vascular surgeons in the department, who decided to serve in the peripheral hospital of Nepal. The lead surgeon of the team was trained in cardiac surgery at G. Pasquinucci Heart Hospital, Massa, Italy and short fellowships in Texas Heart institute and the University of Vienna, and started and maintained the department. A dedicated ICU was setup, protocols were established, and the necessary equipment and drugs were procured. Notably, nitric oxide, papaverin, cardioplegia solution, different valves, and custom packs were initially hard to obtain through the established supply chains as a result of financial restrictions. Apart from cardiac surgery, thoracic and vascular surgery services were rendered to patients, and undergraduate and postgraduate students from the local university were taught.

In a developing country like Nepal, developing cardiac surgery service is a big challenge. As suggested by several studies, there needs to be different modalities of development of this expensive but vital service. Ideally, local cardiac surgery institutions are established to sustainably provide continuous treatment for patients in need in LMICs.[19–21] In Nepal, our modality is functioning by developing our own department with institutional support as well as support from colleagues from abroad. For example, the Cardio Tuscany team from Italy visited through short missions and operating through collaborative models while training the local team; however, the majority of cases were done independently by the local team. Furthermore, surgery charges and consumable and pharmacy charges for cardiac patients have been subsidized significantly by the hospital. Continuing support and collaboration from philanthropists, institutions, cardiologist colleagues from home and abroad, professional societies, and nongovernmental organizations have eased our journey. Nevertheless, a lack of specialized manpower like perfusionists, cardiac anesthetists, and ICU nurses remains a big task. Moreover, setting up the anesthesia services for cardiac surgery proved challenging, with the need to procure special monitors and infusion pumps for the ICU. Notably, issues were observed with the monitoring of arterial lines and central venous pressure lines due to incompatibility of the monitor and the transducers. Initially, an experienced cardiac anesthesiologist from Bangladesh, then from India, and thereafter regularly from Kathmandu was invited, who also trained the local anesthesiologist. After short fellowships and exposure with trained anesthesiologists, the local anesthesiologists were able to perform the cases. A perfusionist, who was trained in India, was hired to manage the heart–lung machine independently. Scrub nurses, ICU nurses, and ward nurses were trained on-the-job in order to manage patients undergoing cardiothoracic and vascular surgery.

Interventional cardiology services are simultaneously developing in LMICs. However, availability of cardiac surgery as a back-up for interventional cardiology is of paramount importance. Around the world, around 85% of patients undergoing coronary angiography undergo angioplasty, out of which the incidence of vascular complications was reported to be between 0.7% and 11.7%.[22] In spite of low incidence of these complications, once it occurs, it is a nightmare for attending cardiologists. At this rare moment, the availability of cardiovascular surgeon is an added luxury for the bail-out procedure. Therefore, successful cardiac programs in peripheral hospital will benefit local patients, cardiologists, and economies in the local area.

Once stated by William Randolph Smith "The road to the heart is only 2-3 cm in length in a direct line, but it has taken surgery nearly 2,400 years to travel it." But, it seems, it will take more than 2,500 years to reach to the poor patients of LMICs.

Conclusion

The enormity of this issue necessitates sense of mission, commitment, enormous enthusiasm, dedication, and clear objectives, supplemented with the sufficient collaborative effort from central and local government, local institutes, cardiologists, non-governmental organizations, international donors, volunteers, and private sponsors. In conclusion, developing cardiac surgery in the peripheral hospitals of LMICs is a strenuous job but with enormous possibility, potential, and rewards.

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References

1. Beck CS. Wounds of the heart. *Arch Surg* 1926; 13: 205–227.
2. Unger F. Worldwide survey on cardiac interventions 1995. *Cor Europaeum* 1999; 7: 128–146.
3. Gaziano TA, Reddy KS, Paccaud F, et al. *Disease control priorities in developing countries*. 2nd ed. New York: World Bank/Oxford University Press, 2006, pp. 645–662.
4. Yacoub M, ElGuindy A, Afifi A, et al. Taking cardiac surgery to the people. *J Cardiovasc Transl Res* 2014; 7: 797–802.
5. Pezzella AT. Global aspects of cardiothoracic surgery with focus on developing countries. *Asian Cardiovasc Thorac Ann* 2010; 18: 299–310.
6. Saxena A. Strategies for the improvement of cardiac care services in developing countries: what does the future hold? *Future Cardiol* 2012; 8: 29–38.
7. Hoffman JIE. The global burden of congenital heart disease. *Cardiovasc J Afr* 2013; 24: 141–145.
8. Musa NL, Hjortdal V, Zheleva B, et al. The global burden of paediatric heart disease. *Cardiol Young* 2017; 27: S3–S8.
9. Global health estimates:deaths by cause, age, sex and country, 2000–2012. Report, World Health Organization, Geneva, 2014.
10. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459–1544.
11. Zühlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015; 36: 1115–1122.
12. Bahadur KC, Sharma D, Shrestha MP, et al. Prevalence of rheumatic and congenital heart disease in schoolchildren of Kathmandu valley in Nepal. *Indian Heart J* 2003; 55: 615–618.
13. Laudari S, Tiwari KK, Pazdernik M, et al. Rheumatic heart disease screening among school children in Central Nepal. *JACC Case Rep* 2019; 1: 218–220.
14. Vaidya A, Pokharel PK, Nagesh S, et al. Prevalence of coronary heart disease in the urban adult males of eastern Nepal: a population-based analytical cross-sectional study. *Indian Heart J* 2009; 61: 341–347.
15. Shah GS, Singh MK, Pandey TR, et al. Incidence of congenital heart disease in tertiary care hospital. *Kathmandu Univ Med J* 2008; 6: 33–36.
16. Vervoort D, Meuris B, Meyns B, et al. Global cardiac surgery: access to cardiac surgical care around the world. *J Thorac Cardiovasc Surg* 2020; 159: 987–996.
17. Neirotti RA. Cardiac surgery: the infinite quest. *Rev Bras Cir Cardiovasc* 2012; 27: 614–620.
18. Al-Khalisi N. The Iraqi medical brain drain: a cross-sectional study. *Int J Health Serv* 2013; 43: 363–378.
19. Novick W, Stidham G, Karl T, et al. Are we improving after 10 years of humanitarian paediatric cardiac assistance. *Cardiol Young* 2005; 15: 379–384.
20. Fenton KN, Castillo SH, Claro CD, et al. Teamwork and program organization in developing countries. *World J Pediatr Congenit Heart Surg* 2011; 2: 219–224.
21. Larrazabal L, Jenkins K, Gauvreau K. Improvement in congenital heart surgery in a developing country: the Guatemalan experience. *Circulation* 2007; 116: 1882–1887.
22. Oweida SW, Roubin GS, Smith RB III, et al. Postcatheterization vascular complications associated with percutaneous transluminal coronary angioplasty. *J Vasc Surg* 1990; 12: 310–315.

Original Paper

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Clinical evaluation of a new dispersive aortic cannula

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Abstract

Introduction: Cerebral injury is a serious complication in open-heart surgery. Once it occurs, it causes significant disability and death. We developed a novel dispersive aortic cannula named the Stealth Flow cannula and used it as a standard aortic cannula in cardiopulmonary bypass. The aim of this study was to evaluate the efficiency of this aortic cannula.

Methods: A total of 182 consecutive patients undergoing cardiac surgery using cardiopulmonary bypass were studied. The patients were divided into two groups: the Soft-Flow cannula group (n = 89) and the Stealth Flow cannula group (n = 93). Patients with a shaggy aortic arch were excluded from this study because the cannulae were inserted at the ascending aorta with a cannula tip directed toward the aortic root in these cases. Patients with multiple arterial perfusion sites were also excluded. Complications including early mortality, perioperative stroke, and intraoperative aortic injury were compared between the two groups.

Results: Age, operative procedure, cardiopulmonary bypass time, and the Japan SCORE were not significantly different between the groups. In comparisons between the Stealth Flow and Soft-Flow groups, the incidences of early mortality, perioperative stroke, intraoperative aortic dissection, and all complications were 1.08% versus 1.12% (p = 0.98), 1.1% versus 2.2% (p = 0.53), 0% versus 1.1% (p = 0.33), and 1.1% versus 3.4% (p = 0.29), respectively. The incidence of major cardiovascular events, including early death, perioperative stroke, and aortic dissection, was not different.

Conclusions: The Stealth Flow cannula, which was designed based on our previous experimental study, contributed to reducing cerebral and aortic events as much as the Soft-Flow cannula in the present clinical study.

Keywords

aortic cannula; clinical evaluation; complications

Introduction

Cerebral injury is an uncommon complication in open-heart surgery. However, once it occurs, it causes significant postoperative disability and death. Causes of cerebral injury are multifactorial: brain hypoperfusion due to perioperative hypotension, occlusive lesions of the carotid-vertebral system, postoperative cardiac arrest, air embolism, fat embolism, and atheroembolism. Age and prolonged cardiopulmonary bypass (CPB) strongly affect the incidence of stroke after heart surgery.[1,2] Carotid and peripheral vascular diseases are strong risk factors. Atheroembolism from a diseased ascending aorta is an emerging problem because aged patients have a high prevalence of atherosclerotic aorta. Manipulation of the diseased aorta induces detachment of atheromatous debris from the aortic cannulation site or aortic clamp site. Another mechanism of atheroembolism is the "sandblast effect" of the jet flow from the aortic cannula tip. We previously reported the effects of the jet flow on normal and diseased aortas in mock aortic models, and we demonstrated that dispersive cannulae were superior to end-hole cannulae from the perspective of the sandblast effect and regurgitant flow from the distal

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aortic arch to the arch vessels.[3] The Soft-Flow cannula model 5767 (3M Cardiovascular, Ann Arbor, MI, USA) is a unique dispersive cannula generating four slender streams. We previously used the Soft-Flow cannula as a standard aortic perfusion cannula for CPB. We developed a novel dispersive aortic cannula called the Stealth Flow cannula® (Toyobo, Osaka, Japan) and have recently used it as a standard aortic perfusion cannula. We previously evaluated the flow characteristics of the Stealth Flow cannula in vitro using a flow visualization method.[4] The aim of the present study was to compare the clinical outcomes of the two dispersive aortic cannulae, the Stealth Flow and the Soft-Flow cannulae. We hypothesized that the Stealth Flow aortic cannula was contributing to reducing cerebral and aortic events as much as the Soft-Flow cannula.

Methods

A total of 182 consecutive adult patients undergoing cardiac surgery using CPB from January 2008 to December 2011 were studied. Patients were classified into two groups by the cannula used: the Soft-Flow cannula (n = 89: from January 2008 to December 2009) and the Stealth Flow cannula (n = 93: from January 2010 to December 2011). The mean age of the patients was 64.9 ± 14.0 years. Patients with a shaggy aortic arch were excluded from this study because the cannulae were inserted at the ascending aorta with the cannula tip directed toward the aortic root in these cases. Patients using multiple arterial perfusion sites including total arch replacement, undergoing surgery for congenital heart disease, and requiring preoperative extracorporeal membrane oxygenation were also excluded. Complications including early mortality, stroke, and cannulation-related aortic injury were compared between the two groups. This study was approved by the research ethics committee of Hirosaki University (approval number 2018-1143).

Preoperative evaluation and surgical protocol

In elective surgery, atherosclerotic disease and calcification of the aorta were evaluated preoperatively by enhanced computed tomography (CT). The grade of the atherosclerosis in the ascending aorta was defined by the aortic thickness, as follows: null (wall thickness <2 mm), mild ($2 \leq$ wall thickness < 4 mm), and moderate (wall thickness ≥ 4 mm). Calcification on the ascending aorta cannulation and aorta clamp site was also evaluated. Carotid and intracranial arterial atherosclerosis were evaluated by magnetic resonance imaging or enhanced CT angiography. Atherosclerotic lesions on the ascending aorta where surgical manipulations were essential were also evaluated both by preoperative imaging and intraoperative epiaortic echo. Then, if a limited atherosclerotic lesion, such as small calcification, sessile atheroma, and small intimal thickness, was found, aortic cannulation and cross-clamping avoiding the area were performed. If there was extensive intimal thickness or a protruding or mobile atherosclerotic lesion on the ascending aorta, ascending aortic cannulation and cross-clamping were not performed in this study.

The same type of CPB circuit was used in all patients. Arterial perfusion pressure of the CPB circuit was monitored. Perfusion pressure was maintained below 300 mm Hg, and the perfusion flow rate was maintained around 2.2-2.6 L/min/m^2. In coronary artery bypass grafting (CABG), a proximal anastomosis to the ascending aorta of the free graft was made during aortic cross-clamping (ACC). Cross-clamping of the ascending aorta was not performed in cases of ascending aorta or aortic arch replacement by open distal anastomosis and in cases of on-pump beating surgeries of pulmonary embolectomy or coronary revascularization.

Aortic cannulae

Two aortic cannulae with cannular tips having the same external diameter (7 mm) were compared. The Stealth Flow cannula has a pentagonal outlet with an obtuse angle creating a flame-like flow (Figure 1(a)). The Soft-Flow cannula has a flow separator on the cannula tip creating a four-directional jet stream (Figure 1(b)).

Statistical analysis

Major adverse cardiovascular events (MACEs) relevant to aortic perfusion were defined as follows: early mortality, postoperative stroke with onset within 24 h, and intraoperative aortic dissection. Postoperative stroke was defined as new cerebral infarction on postoperative brain imaging accompanied by permanent or temporary neurologic dysfunction within 24 h after the operation. Discrete variables are expressed as numbers and percentages. Univariate analysis of mortality or adverse effects was performed using the Mann–Whitney test, chi-square test, or Fisher's exact test, as appropriate. Continuous variables with normal distributions are presented as means and standard deviation. Statistical analysis was performed using SPSS software for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA). P values < 0.05 were regarded as significant.

Results

Patients' characteristics such as age, male sex, hypertension, diabetes mellitus, peripheral artery disease,

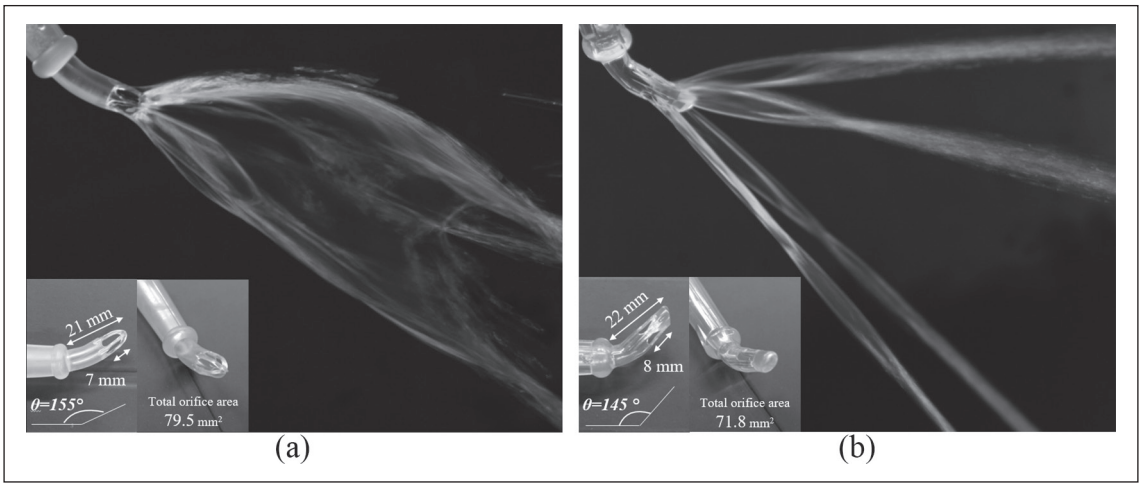

Figure 1. Shape of the cannula tip and the jet flow shape in open air. (a) Stealth Flow cannula and (b) Soft-Flow cannula. Total orifice area of the cannula exit of the Stealth flow cannula and Soft-flow cannula was 79.5 and 71.8 mm^2, respectively. The jet length of the both cannulae was similar and ranging from 100 to 150 mm in the open air.

Table 1. Patient characteristics.

Variable	Total	Cannula		p value
		Stealth Flow	Soft-Flow	
Patients (n)	182	93	89	
Age	64.9 ± 14.0	64.9 ± 12.1	63.8 ± 13.6	0.5288
Male sex	104 (57%)	52 (56%)	52 (58%)	0.7320
Hypertension	104 (57%)	50 (54%)	52 (58%)	0.5263
Diabetes mellitus	39 (21.4%)	15 (16.1%)	24 (26.9%)	0.0749
Peripheral arterial disease	16 (8.8%)	6 (6.5%)	10 (11.2%)	0.2545
Cerebrovascular events	24 (13.2%)	8 (8.6%)	16 (17.9%)	0.0617
Operative procedure				
Valve surgery	149 (81.9%)	79 (84.9%)	70 (78.7%)	0.5450
Coronary surgery	33 (18.1%)	14 (15.1%)	19 (21.3%)	
Cardiopulmonary bypass time (minutes)	184.5 ± 75.8	195.9 ± 83.7	173.7 ± 68.4	0.0474
Aortic cross-clamping time (minutes)	126.5 ± 48.6	132.6 ± 51.2	120.7 ± 45.3	0.1048
Japan SCORE (30-day mortality)	2.49 ± 4.72	2.51 ± 4.8	2.43 ± 4.4	0.6134
Calcification	21 (11.5%)	12 (12.9%)	9 (10.1%)	0.5558
Atherosclerosis				
Null	164 (90.1%)	81 (87.1%)	83 (93.3%)	0.2302
Mild	16 (8.8%)	10 (10.8%)	6 (6.7%)	
Moderate	2 (1.1%)	2 (2.1%)	0 (0%)	

SD: standard deviation.
Data presented as means ± SD or numbers.

cerebrovascular events, operative procedure, ACC time, the Japan SCORE, calcification, and atherosclerosis were not significantly different between the two groups (Table 1). The average CPB time was significantly longer in the Stealth Flow group. The first, second, and third quartiles of the Japan SCORE of the Stealth Flow group were 0.90, 1.40, and 1.80, respectively, whereas those of the Soft-Flow group were 0.90, 1.20, and 2.60, respectively. Early mortality was 1.08% in the Stealth Flow group and 1.12% in the Soft-Flow group ($p = 0.98$). Perioperative stroke (1.1% vs. 2.2%, $p = 0.53$), intraoperative aortic dissection (0% vs. 1.1%, $p = 0.33$), and all cerebrovascular complications (1.1% vs. 3.4%, $p = 0.29$) were not significantly different between the two groups (Table 2). Other complications such as prolonged ventilator use longer than 72 h, maximum postoperative serum creatinine level, intraoperative haptoglobin use, and intensive care unit (ICU) stay were also not significantly

Table 2. Complications and outcomes.

	Stealth Flow (n = 93)	Soft-Flow (n = 89)	p value
Complication	1 (1.1%)	3 (3.4%)	0.2910
Stroke	1 (1.1%)	2 (2.2%)	0.5348
Dissection	0 (0%)	1 (1.1%)	0.3266
Prolonged ventilator use (>72 hours)	9 (9.7%)	11 (12.4%)	0.5630
Serum creatinine (mg/dL)	1.4 ± 0.8	1.3 ± 0.9	0.8368
Intraoperative haptoglobin use	13 (14.0%)	8 (9.0%)	0.2922
ICU stay (days)	3.3 ± 3.0	3.5 ± 5.9	0.7537
30-day mortality	1 (1.08%)	1 (1.12%)	0.9751
MACE	4 (4.30%)	6 (6.74%)	0.4701
[95% CI]	[0.12, 5.0]	[1.1, 7.0]	

ICU: intensive care unit; MACE: major adverse cardiovascular event; CI: confidence interval; SD: standard deviation.
Data presented as means ± SD or numbers.

Table 3. Details of complications of stroke and aortic dissection.

Case	Cannula	Age (years)	Complication	CPB (minutes)	ACC (minutes)	Operative procedure	Cerebral infarction	Atherosclerosis	Calcification	Elective
1	Stealth Flow	64	Stroke	252	189	AVR + CABG (3)	Solitary	No	Yes	Yes
2	Soft-Flow	60	Stroke	97	57	ASD closure + TAP	Solitary	No	No	Yes
3	Soft-Flow	74	Stroke	130	–	On-pump CABG (4)	Multiple	–	–	No
4	Soft-Flow	64	Aortic dissection	159	87	MVR + full Maze	–	No	Mild	Yes

Aortic dissection: acute aortic dissection on the ascending aorta; CPB: cardiopulmonary bypass; ACC: aortic cross-clamping; AVR: aortic valve replacement; CABG (3): coronary artery bypass grafting (3 branches); ASD: atrial septal defect; TAP: tricuspid annuloplasty; CABG (4): coronary artery bypass grafting (4 branches); MVR: mitral valve replacement.

different between the two groups. The incidence of MACE was not significantly different between the two groups.

Details of major cerebrovascular complications are shown in Table 3. In the Stealth Flow group, one patient developed a solitary ischemic stroke at the basal ganglia. The patient presented with temporary motor weakness, but recovered completely afterwards. Causes of early death in the Stealth Flow group were ischemic heart disease in two patients and postoperative ischemic encephalopathy in one patient. Two early deaths in the Soft-Flow group were due to ischemic heart disease and multiple organ failure. Mortality in both groups was not associated with aortic cannula-related complications.

Discussion

Atheroembolism is a major cause of non-cardiac complications following open-heart surgery. Manipulation of the atherosclerotic aorta such as for aortic cannulation and cross-clamping and side-biting clamp application may cause embolism of the atheromatous material into cerebral vessels, visceral arteries, and peripheral arteries. An autopsy study of cerebral pathology after CPB showed atheroembolism in 16.3% of brains.[5] In patients having a severely atheromatous aorta, the perfusion strategy is important because jet flow–induced atheroembolism may be a potential complication in cardiovascular surgery using CPB.[6–11] These emboli may eventually reach the brain through the aortic arch vessels.[12] Cognitive damage after open-heart surgery may be present in nearly three quarters of patients at the time of discharge from the hospital, and it may be present in about one third of patients after 6 months.[2] Dispersive-type aortic cannulae were designed to attenuate the jet flow from the cannula tip. A Soft-Flow arterial perfusion cannula was introduced into clinical use in the early 1990s.[13,14] The concept of this cannula is to split the flow into four streams by four side holes and a cone-shaped flow divider at the tip of the cannula. Dispersed streams have low kinetic energy and decelerate within several centimeters from the exit, avoiding the sandblast effect due to jet flow.[6]

We designed a new type of aortic cannula called the Stealth Flow aortic cannula, characterized by a pentagonal outlet with an obtuse angle creating flame-like flow to reduce the focal high-velocity jet flow seen with the Soft-Flow cannula.[4] In experimental evaluation by particle image velocimetry using a mock thoracic aorta, the maximum exit flow velocities of both cannulae were similar (Stealth Flow, 0.68 m/s vs. Soft-Flow cannula, 0.60 m/s), but the velocity and vortex near the arch vessels in the

Stealth Flow cannula were attenuated compared to those in the Soft-Flow cannula.

Grooters et al. compared the flow velocity from a straight end-hole cannula, the Soft-Flow cannula, and a Dispersion (Edwards Lifesciences LLC, Irvine, CA, USA) cannula in the aorta using duplex flow velocimetry and showed that a dispersive type aortic cannula would be beneficial in reducing the sandblast effect by attenuating intra-aortic cannular flow. Furthermore, Grooters et al.[15,16] also reported that cannular insertion toward the aortic root using a Dispersion cannula could avoid disruption of the atherosclerotic intima on the aortic arch and reported satisfactory clinical outcomes in patients undergoing CABG. Yamana et al.[17] evaluated the Dispersion cannula in vivo using transesophageal echocardiography (TEE) and demonstrated that perfusion toward the aortic valve resulted in a significantly decreased peak flow velocity in the aortic arch during CPB. Then, Fukuda et al.[18] suggested that, in atherosclerotic aortic arch aneurysms, central cannulation under ultrasound guidance along with directing the dispersive cannula toward the aortic root is a simple and effective perfusion strategy. Minakawa et al.[3,19] compared flow velocity and shear stress in a mock aortic model of the normal aorta and an aorta with an aneurysm of the arch. They found that an end-hole cannula should not be used in an atherosclerotic aorta.

Studies of aortic cannulae using an experimental circuit and simulations have been reported, but clinical data have been sparse.[20–22] The present study was a clinical comparison of two aortic cannulae designed to have decreased shear stress on the aortic wall through dispersive exit flow into the aorta. Although there was no significant difference in MACE between the two groups, previous experimental data showed that the exit flow from the Stealth Flow would cause less shear stress on the aortic wall than that from the Soft-Flow cannula.[4] The incidence of stroke and aortic dissection was low in the Stealth Flow group, demonstrating the potential that the Stealth Flow cannula will contribute to reducing cannula-related adverse perioperative events.

The limitations of this study were (1) the number of cases was small in a single center, (2) it was a retrospective study with patients not randomized to the two groups, and (3) surgeon, atherosclerotic grade or lesion, and cannulation site of the ascending aorta were different in each case. Although the postoperative outcomes of stroke and iatrogenic aortic dissection were not significantly different between the two groups, further randomized evaluation will be necessary to determine the superiority of the Stealth Flow cannula.

Conclusion

The Stealth Flow cannula, which was designed based on our previous experimental study, contributed to reducing cerebral and aortic events as much as the Soft-Flow cannula in the present clinical study.

Author contributions

All authors have made substantial contributions to all the following: T.G., I.F., K.D., and M.M. helped in the conception and design of the study; Y.K., A.T., T.O., J.O., and T.G. helped in acquisition of data; and R.K. and K.Y. helped in analysis and interpretation of data. T.G., M.M., and I.F. helped in drafting the article or revising it critically for important intellectual content. All authors provided approval for the final version to be submitted.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: I.F. is an inventor of the Stealth Flow cannula. All other authors declare that they have no conflicts of interest.

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References

1. Culliford AT, Colvin SB, Rorher K, et al. The atherosclerotic ascending aorta and transverse arch: a new technique to prevent cerebral injury during bypass: experience with 13 patients. *Ann Thorac Surg* 1986; 41: 27–35.
2. Katz ES, Tunick PA, Rusinek H, et al. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. *J Am Coll Cardiol* 1992; 20: 70–77.
3. Minakawa M, Fukuda I, Yamazaki J, et al. Effect of cannula shape on aortic wall and flow turbulence: hydrodynamic study during extracorporeal circulation in mock thoracic aorta. *Artif Organs* 2007; 31: 880–886.
4. Goto T, Inamura T, Shirota M, et al. Hydrodynamic evaluation of a new dispersive aortic cannula (Stealthflow). *J Artif Organs* 2016; 19: 121–127.
5. Blauth CI, Cosgrove DM, Webb BW, et al. Atheroembolism from the ascending aorta. An emerging problem in cardiac surgery. *J Thorac Cardiovasc Surg* 1992; 103: 1104–1111; discussion 1111–1112.
6. Wareing TH, Davila-Roman VG, Barzilai B, et al. Management of the severely atherosclerotic ascending aorta during cardiac operations. *J Thorac Cardiovasc Surg* 1992; 103: 453–462.
7. Weinstein GS. Left hemispheric strokes in coronary surgery: implications for end-hole aortic cannulas. *Ann Thorac Surg* 2001; 71: 128–132.
8. Van Der Linden J, Hadjinikolaou L, Bergman P, et al. Postoperative stroke in cardiac surgery is related to the

location and extent of atherosclerotic disease in the ascending aorta. *J Am Coll Cardiol* 2001; 38: 131–135.
9. Hogue CW, Murphy SF, Schechtman KB, et al. Risk factors for early or delayed stroke after cardiac surgery. *Circulation* 1999; 100: 642–647.
10. Salazar JD, Wityk RJ, Grega MA, et al. Stroke after cardiac surgery: short- and long-term outcomes. *Ann Thorac Surg* 2001; 72: 1195–1201; discussion 1201–1202.
11. Ura M, Sakata R, Nakayama Y, et al. Ultrasonographic demonstration of manipulation-related aortic injuries after cardiac surgery. *J Am Coll Cardiol* 2000; 35: 1303–1310.
12. Fukuda I, Minakawa M, Fukui K, et al. Breakdown of atheromatous plaque due to shear force from arterial perfusion cannula. *Ann Thorac Surg* 2007; 84: e17–e18.
13. Muehrcke DD, Cornhill JF, Thomas JD, et al. Flow characteristics of aortic cannulae. *J Card Surg* 1995; 10: 514–519.
14. Grossi EA, Kanchuger MS, Schwartz DS, et al. Effect of cannula length on aortic arch flow: protection of the atheromatous aortic arch. *Ann Thorac Surg* 1995; 59: 710–712.
15. Grooters RK, Ver Steeg DA, Stewart MJ, et al. Echocardiographic comparison of the standard end-hole cannula, the soft-flow cannula, and the dispersion cannula during perfusion into the aortic arch. *Ann Thorac Surg* 2003; 75: 1919–1923.
16. Grooters RK, Thieman KC, Schneider RF, et al. Assessment of perfusion toward the aortic valve using the new dispersion aortic cannula during coronary artery bypass surgery. *Tex Heart Inst J* 2000; 27: 361–365.
17. Yamana K, Ito T, Maekawa A, et al. Atherosclerotic arch aneurysm operations with perfusion toward the aortic valve. *Ann Thorac Surg* 2010; 89: 435–439.
18. Fukuda I, Daitoku K, Minakawa M, et al. Shaggy and calcified aorta: surgical implications. *Gen Thorac Cardiovasc Surg* 2013; 61: 301–313.
19. Minakawa M, Fukuda I, Igarashi T, et al. Hydrodynamics of aortic cannulae during extracorporeal circulation in a mock aortic arch aneurysm model. *Artif Organs* 2010; 34: 105–112.
20. Darlis N, Osman K, Padzillah MH, et al. Modification of aortic cannula with an inlet chamber to induce spiral flow and improve outlet flow. *Artif Organs* 2018; 42: 493–499.
21. Kaufmann TAS, Schlanstein P, Moritz A, et al. Development of a hemodynamically optimized outflow cannula for cardiopulmonary bypass. *Artif Organs* 2014; 38: 972–978.
22. Fukuda I, Yanaoka H, Inamura T, et al. Experimental fluid dynamics of transventricular apical aortic cannulation. *Artif Organs* 2010; 34: 222–224.

Original Paper

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Thrombotic risk in central venoarterial extracorporeal membrane oxygenation post cardiac surgery

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Abstract

Introduction: Post-cardiotomy cardiogenic shock is an accepted indication for venoarterial extracorporeal membrane oxygenation. The true incidence and risk factors for the development of thrombosis in this setting remain unclear.

Methods: Patients supported with central venoarterial extracorporeal membrane oxygenation due to ventricular dysfunction precluding weaning from cardiopulmonary bypass were retrospectively identified. Electronic records from a single institution spanning a 4-year period from January 2015 to December 2018 were interrogated to assess the incidence of thrombosis. The relationship to exposures including intracardiac stasis and procoagulant usage was explored.

Results: Twenty-four patients met the inclusion criteria and six suffered major intracardiac thrombosis. All cases of thrombosis occurred early, and none survived to hospital discharge. The lack of left ventricular ejection conferred a 46% risk of developing thrombosis compared to 0% if ejection was maintained ($p = 0.0093$). Aprotinin use was also associated with thrombus formation ($p = 0.035$). There were no significant differences between numbers of patients receiving other procoagulants when grouped by thrombosis versus no thrombosis.

Conclusion: Stasis is the predominant risk factor for intracardiac thrombosis. This occurs rapidly and the outcome is poor. As a result, we suggest early left ventricular decompression. Conventional management of post-bypass coagulopathy seems safe if the aortic valve is opening.

Keywords

ECMO; coagulation; thrombosis; cardiogenic shock; cardiopulmonary bypass

Introduction

Extracorporeal membrane oxygenation (ECMO) is increasingly used during cardiac surgery in case of failure to wean patients from cardiopulmonary bypass (CPB).[1,2] This can provide a bridge to decision, recovery, long-term mechanical support, or transplantation. Central ECMO is frequently applied, taking advantage of the atrial drainage and ascending aorta return cannulas already used during CPB.[3,4] The major differences from CPB are a simpler circuit with less blood contacting nonendothelial surfaces per unit time, and the absence of an open reservoir.[5] The sternum can then be left open, or closed with subxiphoid tunneling of the cannulas.[4] Peripheral cannulation is advocated by some groups and no definitive advantage of either configuration has been demonstrated.[6,7]

A recent review from the authors' institution found that 0.55% of patients were supported with central venoarterial ECMO (C-VA-ECMO) following cardiac surgery.[8] Of these, 62% were initiated on ECMO prior to leaving the operating theater.[8] The most common indication is post-cardiotomy cardiogenic shock refractory to ionotropic support and intra-aortic balloon counterpulsation. Persistent hypoxemia, sometimes with coexistent biventricular or isolated right ventricular failure, is an alternate rationale in specific settings. Multiple meta-analyses have demonstrated a successful decannulation rate of 57% to 60% with survival to hospital

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discharge ranging from 30% to 36%.[9–11] Although survival remains limited, these figures suggest substantial advantage in what is otherwise a terminal scenario.

ECMO is resource intensive and numerous contemporary studies have rightly focused on improving outcomes via refining the indications for post-cardiotomy ECMO.[3,8,12,13] Prevention of complications, however, has received less emphasis but is equally likely to provide incremental benefits. Major hemorrhage is consistently reported as one of the most frequent complications of post-cardiotomy central VA-ECMO with rates of re-thoracotomy for bleeding approximating 50%.[3,11] Intracardiac thrombosis is less prevalent, but almost always fatal. Reported incidence is in the range of 4-5%.[8,14]

Most publications have elaborated on outcomes: survival to weaning of circulatory support and hospital discharge, but little on detailed management. Remarkably little is published on the management of post-bypass coagulopathy with concurrent initiation of VA-ECMO. Most of what is known reflects intensive care rather than operating room management and there is no guidance on how best to achieve the optimal balance between excessive bleeding and thrombosis after transitioning from CPB.[5,15] Risk of bleeding in the immediate post-surgical setting is intuitive, but the conditions for thrombus formation can co-exist. Major surgery and the blood–biomaterial interaction activate complex coagulation and inflammatory pathways disrupting normal hemostatic homeostasis.[16] In addition, multiple procoagulant substances are commonly administered and there is the potential for stasis. Both are readily modifiable.

The objectives of this retrospective investigation were to examine the management of intracardiac stasis as well as the safety of procoagulant products used around the time of transition from CPB to C-VA-ECMO. Specifically, the authors identified all procoagulants used as well as the presence or absence of cardiac ejection. An association was sought between the administration of multiple procoagulants or intracardiac stasis and early thrombosis.

Methods

Study design

After gaining institutional review board's (IRB) approval (no. S02528), this retrospective cohort study was conducted in a single tertiary cardiothoracic center. It is one of six centers offering heart transplantation in the United Kingdom as well as providing the sole national pulmonary endarterectomy service. We perform approximately 2000 CPB cases per year, with 15-20 patients annually supported with ECMO post-operatively. A further 10-15 runs of VA-ECMO are performed for cardiogenic shock unrelated to surgery. Venovenous (VV) ECMO for isolated respiratory failure is more common with 50-70 patients supported per year. A 4-year period from the start of 2015 through to the end of 2018 was examined.

Participants

Patients supported with C-VA-ECMO following cardiac surgery were identified from interrogation of the prospectively kept, detailed perfusion database.

The inclusion criterion was as follows:

C-VA-ECMO had to be initiated in the same operative episode as the index operation due to inability to wean from CPB as a result of left, right, or biventricular dysfunction.

The exclusion criteria were as follows:

C-VA-ECMO initiated intraoperatively where the primary indication was not ventricular dysfunction;

Patients who had ECMO instituted due to deterioration in the post-operative phase after transfer from the operating theater;

C-VA-ECMO for support of heart failure patients from the intensive care unit;

Peripheral configurations of VA-ECMO.

Outcomes

The primary outcome was major thrombosis occurring within 24 hours of C-VA-ECMO initiation. This was defined as intracardiac thrombus identified on transoesophageal echocardiography (TOE) with or without concurrent thrombosis of the ECMO circuit. The timeframe was chosen to limit confounding from variations in post-operative management.

Data were also collected on whether ECMO was weaned successfully or not and survival to hospital discharge. These were added for the purpose of enhancing the external validity of the results rather than to examine any association with exposures.

Exposures

Investigated risk factors for thrombosis included intracardiac stasis and procoagulants administered intraoperatively. Intracardiac stasis was identified preferentially by the absence of aortic valve (AV) opening on TOE. When this information was not available, an arterial pulse pressure of no less than 15 mmHg was used as a surrogate (in the absence of an intra-aortic balloon pump (IABP)) as it has been suggested that a pulse pressure of

approximately 10 mmHg can be taken to represent the heart pumping about 20% of the circulating volume.[17] Finally, documented comment on non-pulsatile flow from the perfusion database was used as confirmation.

Procoagulants identified included antifibrinolytics, fractionated blood components, factor concentrates, and protamine. Protamine effect was quantified via post-protamine activated clotting time (ACT) and the heparin-to-protamine ratio. Heparin-to-protamine ratio was based on the total dose of heparin administered excluding 5000 units used as part of the bypass circuit prime. Recent investigations suggest that a heparin-to-protamine ratio between 0.6 and 1.0 may be optimal.[18,19]

Antifibrinolytics utilized included tranexamic acid and aprotinin. Tranexamic acid was administered either as a 2-g bolus pre-CPB or as a 1-g bolus and a 500-mg-per-hour infusion until the end of the operation (as per departmental protocol). We used the Hammersmith protocol for aprotinin administration with a test dose of 10,000 kallikrein inhibitor units (KIU), followed by a loading dose of 2 million KIU, with a further 2 million KIU added to the pump prime and a continuous infusion of 500,000 KIU per hour regardless of body weight for the duration of the operation. Both drugs are administered at the discretion of the attending anesthetist and surgeon in charge of the case. Aprotinin use is restricted to patients with perceived high risk of bleeding such as redo surgery, emergency aortic arch surgery, or active endocarditis.

When administered, a four-factor prothrombin complex concentrate, Beriplex (CSL Behring, UK), was used and RiaSTAP (CSL Behring, UK) was the fibrinogen concentrate. Actual body weight was utilized for dose calculations of fractionated blood products.

Clearly, a multitude of other factors contribute to post-bypass coagulopathy such as pre-operative comorbidities and medication usage, CPB duration, temperature, acid-base status, calcium levels, red blood cell, and cell saver transfusion. These potential confounders were not measured as our observations aimed to inform the practical objective of administering procoagulants rather than attempt to define the degree of coagulopathy.

Data sources

Data were sourced from a variety of electronic records including anesthetic and perfusion charts, TOE reports or images, operation notes, intensive care, and hospital discharge summaries. Extracted data were de-identified and manually entered in a database.

Analysis

Patients were grouped by primary outcome and details of exposures tabulated accordingly. Differences in risk of developing early thrombosis according to exposures were calculated and associations tested for statistical significance with two-sided Fisher's exact tests. All statistical analyses were performed using STATA version 14.2 (StataCorp LP, College Station, TX, USA).

Results

A total of 61 patients supported with VA-ECMO post-bypass were identified. Of these, 22 were excluded due to delayed insertion following post-operative deterioration and 2 because of a peripheral configuration. In three cases, documentation was missing or inadequate. A further 10 were excluded as pulmonary hemorrhage secondary to a pulmonary artery breach was the primary indication. These patients came from the pulmonary thromboendarterectomy (PTE) population where C-VA-ECMO is used to provide respiratory and often right ventricular support, but importantly, also to decompress the pulmonary circulation. Data for the remaining 24 subjects where C-VA-ECMO was used due to inability to wean from CPB as a result of ventricular dysfunction are presented.

Outcome data including thrombosis, successful decannulation, and survival to hospital discharge rate are shown in Table 1. The two heart transplant patients changed to alternate support included one to a temporary biventricular assist device (BiVAD) on Day 1 post-operatively and another to a temporary right ventricular assist device (RVAD) on Day 13.

Six cases of thrombosis were identified, and all had major left-sided intracardiac thrombus formation. A representative example is illustrated in Figure 1. Three had concurrent abrupt loss of drainage on ECMO, likely due to thrombosis. Left atrial (LA) thrombus was present in five cases. In three of these, left ventricular (LV) thrombus was also identified, two of which had additional thrombus in the left ventricular outflow tract (LVOT), and aortic root involvement in one. There was one case of isolated LV thrombus. In five of the six cases, thrombus developed within 1 hour of ECMO initiation. In another, it was noted some hours later in the intensive care unit prompting a return to theater 12 hours post-operatively for conversion to a temporary BiVAD. In four cases of thrombosis, the patient died on the operating table. Support was withdrawn on Day 2 post-operatively for another due to futility. The patient converted to a BiVAD suffered a terminal neurologic event 2 weeks post-operatively.

Stasis as a risk factor for thrombosis is examined in Table 2. Despite all patients receiving pharmacological inotropic support and 69% having an IABP in situ, pulsatility was only able to be confirmed in 11 cases. Lack of LV ejection conferred a 46% (95% CI = 19-73) risk of developing thrombosis. Fisher's exact test demonstrated that there is a statistically significant association between non-pulsatility and thrombus formation ($p = 0.0162$).

Table 1. Outcome data for patients supported with central venoarterial extracorporeal membrane oxygenation for ventricular dysfunction post cardiac surgery.

	Cases	Outcome					
		Thrombosis		Decannulation		Discharged alive	
		n	%	n	%	n	%
CABG	5	0	0	3	60	1	20
CABG + valve	7	2	29	2	29	0	0
Aortic	3	2	67	0	0	0	0
PTE	3	0	0	0	0	0	0
Transplant	6	2	33	4[a]	67	2	33
Total	24	6	25	9	38	3	13

CABG: coronary artery bypass grafting; PTE: pulmonary thromboendarterectomy.
[a]Includes n = 2 changed to alternate mechanical support.

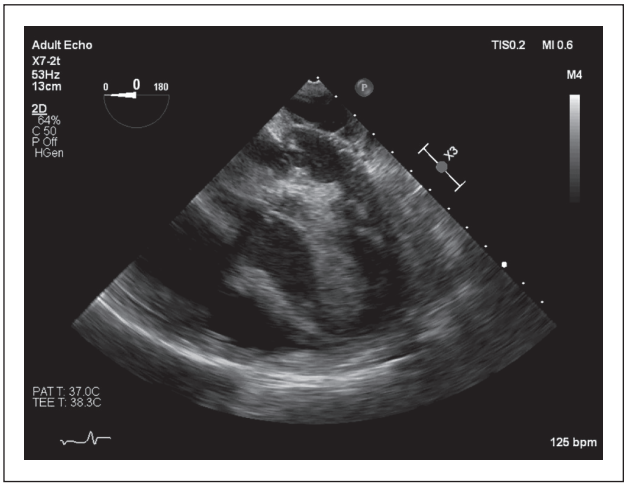

Figure 1. Midoesophageal four-chamber view demonstrating extensive left ventricular intracavity thrombosis.

One case was re-heparinized with 265 units/kg once absence of AV opening with associated spontaneous echo contrast was identified on TOE. Thrombosis did not develop in this patient, although he bled profusely in the intensive care unit and ultimately care was withdrawn on Day 5 due to futility. Only one patient with a non-ejecting heart at the time of ECMO initiation was successfully decannulated and there were no survivors to hospital discharge.

Absolute number and proportions of patients exposed to procoagulants in relation to thrombotic outcome is displayed in Table 3. All patients received an antifibrinolytic medication and aprotinin was found to be significantly associated with thrombosis ($p = 0.035$). Tranexamic acid appeared protective, although this can be explained by the absence of aprotinin. No other significant associations were able to be demonstrated.

Table 4 shows that when administered, the mean dose of the respective procoagulants was also similar between groups. Heparin was fully reversed in all patients with the lowest heparin-to-protamine ratio being 0.67. No patient received recombinant Factor VIIa.

Table 2. Presence or absence of left ventricular ejection and intracardiac thrombosis.

	No LV ejection	LV ejection	Total
Thrombosis	6	0	6
No thrombosis	7	11	18
Total	13	11	24
Risk difference	0.46		
95% CI	0.19-0.73		
p-value	0.016		

LV: left ventricular; CI: confidence interval.

Discussion

It must be born in mind that post-operative ECMO is a desperate measure and without the support, all patients included in this investigation would have died on the operating table. There is a fine balance between achieving hemostasis and risking thrombotic complications. The decision whether to vent a poorly contracting heart is also a difficult one. It requires the introduction of an additional cannula which complicates the circuit and increases the potential bleeding risk. However, it decompresses the LV and reduces stasis.[4]

Our data demonstrate a concerningly high rate of major intracardiac thrombosis after C-VA-ECMO institution following failure to wean from CPB due to ventricular dysfunction. This occurs rapidly and the outcome is universally poor. The major risk factor seems to be lack of native cardiac ejection leading to stasis and potentially distension of the left-sided heart chambers. Conversely, it appears safe to treat post-bypass coagulopathy in a conventional manner if there is residual cardiac function while on C-VA-ECMO.

Table 3. Number and proportion of patients receiving procoagulants and risk of intracardiac thrombosis.

Procoagulants		Thrombosis				Risk difference	95% CI	p-value
		Y (n = 6)		N (n = 18)				
		n	%	n	%			
Antifibrinolytic	Tranexamic acid	3	50	17	94	−0.6	−1.05 to −0.15	0.035
	Aprotinin	3	50	1	6	0.6	0.15 to 1.05	0.035
Fresh frozen plasma		4	67	9	50	0.13	−0.21 to 0.46	0.649
Platelets		4	67	15	83	−0.19	−0.65 to 0.28	0.568
Cryoprecipitate		3	50	4	22	0.25	−0.16 to 0.66	0.307
Prothrombin complex concentrate		3	50	4	22	0.25	−0.16 to 0.66	0.307
Fibrinogen concentrate		1	17	7	39	−0.19	−0.51 to 0.14	0.621

CI: confidence interval.

Table 4. Mean dose of procoagulants when administered and details of heparin reversal.

Procoagulants	Thrombosis	No thrombosis
Fresh frozen plasma (mL/kg)	25	22
Platelets (mL/kg)	5.8	5.8
Cryoprecipitate (mL/kg)	4.8	6.8
Prothrombin complex concentrate (units)	1750	2075
Fibrinogen concentrate (g)	4	4
Post-protamine ACT	157	147
Heparin-to-protamine ratio	1.2	1.1

ACT: activated clotting time.

The 25% incidence of thrombosis in our cohort is higher than previously reported. Furthermore, this represents a minimum rate as no systematic screening was performed and less clinically dramatic events may have been missed. It is important to highlight that these were all intracardiac thromboses, although in three cases there was also sudden loss of venous drainage to the ECMO circuit at around the same time. We can only speculate whether this was due to unrecognized right-sided intracardiac thrombosis or clots forming within the circuit. At the end of a long period on bypass, high ECMO flow is desired to perfuse the peripheral tissues and reverse acidosis, but this also diminishes the RV preload and possibility for ejection. Thus, while high circuit flow can minimize the risk of circuit thrombosis, this may paradoxically increase the risk of intracardiac thrombosis.[5] Where possible, lower ECMO flows and slower achievement of homeostasis could allow RV ejection.

The high rate of thrombosis in this study may reflect our delayed management of LV stasis, but two alternate explanations can also be entertained. First, we present a more homogeneous cohort with deliberate exclusion of cases where C-VA-ECMO was initiated in the post-operative period, thereby selecting a group with the most severe myocardial dysfunction. The second possibility is that previously reported low rates of clinically apparent thrombosis might not be reflective of the true incidence. Lending support to this, an autopsy study of patients who died following post-cardiotomy ECMO found evidence of systemic thromboembolic events in 70%.[20]

Stasis was the predominant risk factor for thrombosis with 46% of patients without pulsatility progressing to develop intracardiac thrombosis. This concept is corroborated by previous reports. Two recent case series totaling nine patients supported with ECMO due to cardiogenic shock described intracardiac or aortic root thrombus formation in the setting of non-ejecting hearts despite adequate anticoagulation.[21,22] However, the majority of these were non-surgical patients and managed with peripheral VA-ECMO. A further case report described LV thrombus in an akinetic LV supported with C-VA-ECMO following AV replacement.[23] This occurred despite heparin anticoagulation being commenced on post-operative Day 1.[23] Interestingly, in this report, the LV thrombus was only identified on Day 4 post-operatively despite daily transthoracic echocardiograms.[23] A review incorporating 12 case reports describes intracardiac thrombus formation despite heparin anticoagulation, but the presence or absence of pulsatility was not defined.[24] There was marked heterogeneity in these cases with a minority being post-cardiotomy. However, a mean time to diagnosis of 3 days was reported.[24] The rapidity of thrombus formation in our study with five of the six cases occurring

within 1 hour and the remaining one within 12 hours has marked clinical relevance.

Even without thrombosis, stasis is a poor prognostic marker with no survivors to hospital discharge in our cohort. This may reflect unrecoverable myocardium, but related complications are also a plausible explanation for the adverse outcomes. A non-ejecting heart will continue to distend due to ongoing bronchial and Thebesian venous flow. As a result, left ventricular end diastolic pressure (LVEDP) will continue to rise, lowering the pressure gradient for coronary perfusion and potentially causing ongoing ischemia in a heart which is supposed to be "rested." Another consequence of elevated LVEDP is the development of pulmonary edema, further decreasing the probability of successful decannulation.

LV decompression strategies have been comprehensively outlined in recent reviews.[25,26] Direct LV venting is usually the most practical option in the post-cardiotomy setting. While a non-ejecting heart is often considered an indication for venting, there remains no consensus on patient selection, timing, or methodology.[26,27] Attempts were made in our cohort with inotropic support, titration of ECMO flows, and IABP insertion in the majority, but none received an LV vent concurrently with ECMO initiation. The rate of early catastrophic intracardiac thrombosis adds significant weight to the a rgument for and urgency of venting. We advocate this being established prior to the reversal of systemic anticoagulation.

In contrast to intracardiac stasis, full heparin reversal and the administration of fractionated blood components or factor concentrates do not seem to increase the risk of major thrombosis in isolation. Patients in whom we found no major thrombotic complications received comparable amounts of procoagulants to those who suffered this fate. Aprotinin is a possible exception and a recent case series highlighted this concern.[28] However, our data incorporated the same three patients from this series and therefore our results provide little further guidance on this issue. Scant details pertaining to heparin reversal and the management of post-bypass coagulopathy can be found in prior reports. We are not aware of any other studies which have specifically evaluated the safety of procoagulants with C-VA-ECMO initiation in the post-cardiotomy population. Given the consistently high rates of bleeding complications, the lack of an obvious association between procoagulant use and thrombosis is reassuring.

Several limitations to our findings should be acknowledged. First, as with any retrospective study, the quality of data extracted is entirely dependent on the quality of the input data. However, these cases are frequently the subject of high levels of scrutiny, which usually prompts accurate documentation; any blood products administered and the appropriate recording of this are the subject to scrupulous audit. We are unable to account for multiple potential confounding variables pertaining to post-bypass coagulopathy, but do not believe that this detracts from the practical question of whether it is safe to administer procoagulants. There is no post-cardiotomy VA-ECMO coagulation protocol in place at our institution. The risk of bleeding, giving clotting products, and thrombotic complications is weighed by the clinical team on an individual basis according to patients' requirements. In general, after the immediate post-operative period when more prolonged support is indicated and in the absence of bleeding complications or coagulopathy, we aim to anticoagulate patients using an unfractionated heparin infusion. The timing of this is decided by a multidisciplinary approach and is tailored to the individual patient requirements bearing in mind the fine balance between hemorrhagic and thrombotic complications. Post-operative VA-ECMO is also a rare event and the numbers in this cohort are correspondingly limited. Finally, our results cannot necessarily be generalized to other indications for or configurations of VA-ECMO.

In summary, we have presented a cohort of 24 patients commenced on C-VA-ECMO for failure to wean from CPB over a 4-year period at a single institution. We report a rate of intracardiac thrombosis of 46% in non-ejecting hearts. None of these patients survived to hospital discharge. Considering the speed of thrombus development, we suggest early LV venting if the AV is not opening. If pulsatility can be maintained, the administration of procoagulants does not appear to be independently associated with intracardiac thrombosis.

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Declaration of Conflicting Interests

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References

1. Karagiannidis C, Brodie D, Strassmann S, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med* 2016; 42: 889–896.
2. Sauer CM, Yuh DD, Bonde P. Extracorporeal membrane oxygenation use has increased by 433% in adults

in the United States from 2006 to 2011. *ASAIO J* 2015; 61: 31–36.
3. Rastan AJ, Dege A, Mohr M, et al. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg* 2010; 139: 302–311, 311.e1.
4. Pavlushkov E, Berman M, Valchanov K. Cannulation techniques for extracorporeal life support. *Ann Trans Med* 2017; 5: 70.
5. Murphy DA, Hockings LE, Andrews RK, et al. Extracorporeal membrane oxygenation-hemostatic complications. *Transfus Med Rev* 2015; 29: 90–101.
6. Saeed D, Stosik H, Islamovic M, et al. Femoro-femoral versus atrio-aortic extracorporeal membrane oxygenation: selecting the ideal cannulation technique. *Artif Organs* 2014; 38: 549–555.
7. Wu MY, Lin PJ, Lee MY, et al. Using extracorporeal life support to resuscitate adult postcardiotomy cardiogenic shock: treatment strategies and predictors of short-term and midterm survival. *Resuscitation* 2010; 81: 1111–1116.
8. Rubino A, Costanzo D, Stanszus D, et al. Central veno-arterial extracorporeal membrane oxygenation (C-VA-ECMO) after cardiothoracic surgery: a single-center experience. *J Cardiothorac Vasc Anesth* 2018; 32: 1169–1174.
9. Khorsandi M, Dougherty S, Bouamra O, et al. Extracorporeal membrane oxygenation for refractory cardiogenic shock after adult cardiac surgery: a systematic review and meta-analysis. *J Cardiothorac Surg* 2017; 12: 55.
10. Wang L, Wang H, Hou X. Clinical outcomes of adult patients who receive extracorporeal membrane oxygenation for postcardiotomy cardiogenic shock: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2018; 32: 2087–2093.
11. Biancari F, Perrotti A, Dalen M, et al. Meta-analysis of the outcome after postcardiotomy venoarterial extracorporeal membrane oxygenation in adult patients. *J Cardiothorac Vasc Anesth* 2018; 32: 1175–1182.
12. Saxena P, Neal J, Joyce LD, et al. Extracorporeal membrane oxygenation support in postcardiotomy elderly patients: the mayo clinic experience. *Ann Thorac Surg* 2015; 99: 2053–2060.
13. Guihaire J, Dang Van S, Rouze S, et al. Clinical outcomes in patients after extracorporeal membrane oxygenation support for post-cardiotomy cardiogenic shock: a single-centre experience of 92 cases. *Interact Cardiovasc Thorac Surg* 2017; 25: 363–369.
14. Slottosch I, Liakopoulos O, Kuhn E, et al. Outcomes after peripheral extracorporeal membrane oxygenation therapy for postcardiotomy cardiogenic shock: a single-center experience. *J Surg Res* 2013; 181: e47–e55.
15. Lo Coco V, Lorusso R, Raffa GM, et al. Clinical complications during veno-arterial extracorporeal membrane oxigenation in post-cardiotomy and non post-cardiotomy shock: still the Achille's heel. *J Thorac Dis* 2018; 10: 6993–7004.
16. Annich G, Barbaro R, Cornell T, et al. Adverse effects of extracorporeal life support: the blood biomaterial interaction. In: Brogan T, Laquier L, Lorusso R, et al. (eds) *Extracorporeal life support: The ELSO red book*. 5th ed. Ann Arbor, MI: ELSO, 2017, pp. 81–92.
17. Bartlett R, Conrad S. The physiology of extracorporeal life support. In: Brogan T, Laquier L, Lorusso R, et al. (eds) *Extracorporeal life support: The ELSO red book*. Ann Arbor, MI: ELSO, 2017, pp. 31–48.
18. Boer C, Meesters MI, Veerhoek D, et al. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. *Br J Anaesth* 2018; 120: 914–927.
19. Kunz SA, Miles LF, Ianno DJ, et al. The effect of protamine dosing variation on bleeding and transfusion after heparinisation for cardiopulmonary bypass. *Perfusion* 2018; 33: 445–452.
20. Rastan AJ, Lachmann N, Walther T, et al. Autopsy findings in patients on postcardiotomy extracorporeal membrane oxygenation (ECMO). *Int J Artif Organs* 2006; 29: 1121–1131.
21. Hireche-Chikaoui H, Grubler MR, Bloch A, et al. Nonejecting hearts on femoral veno-arterial extracorporeal membrane oxygenation: aortic root blood stasis and thrombus formation: a case series and review of the literature. *Crit Care Med* 2018; 46: e459–e464.
22. Alhussein M, Moayedi Y, Posada JD, et al. Ventricular thrombosis post-venoarterial extracorporeal membrane oxygenation. *Circ Heart Fail* 2017; 10: e003757.
23. Porizka M, Kopecky P, Mikulenka V, et al. Catastrophic left ventricular thrombosis complicating extra-corporeal membrane oxygenation: a case report. *Prague Med Rep* 2017; 118: 139–146.
24. Williams B, Bernstein W. Review of venoarterial extracorporeal membrane oxygenation and development of intracardiac thrombosis in adult cardiothoracic patients. *J Extra Corpor Technol* 2016; 48: 162–167.
25. Donker DW, Brodie D, Henriques JPS, et al. Left ventricular unloading during veno-arterial ECMO: a review of percutaneous and surgical unloading interventions. *Perfusion* 2019; 34: 98–105.
26. Xie A, Forrest P, Loforte A. Left ventricular decompression in veno-arterial extracorporeal membrane oxygenation. *Ann Cardiothorac Surg* 2019; 8: 9–18.
27. Ma C, Tolpin D, Anton J. Con: patients receiving venoarterial extracorporeal membrane oxygenation should not always have a left ventricular vent placed. *J Cardiothorac Vasc Anesth* 2019; 33: 1163–1165.
28. Oscier C, Patvardhan C, Falter F, et al. Three consecutive cases of fatal intraoperative intracardiac thrombosis associated with the initiation of venoarterial extracorporeal membrane oxygenation in the presence of aprotinin. *Perfusion* 2019; 34: 417–421.

Original Paper

Perfusion

Comparison of three autotransfusion devices for utilization in the pediatric population

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Abstract

Introduction: A device that may help attenuate the amount of homologous blood product given to pediatric cardiac surgical patients is the autotransfusion device. Three separate autotransfusion devices were selected for evaluation. The Sorin Xtra, Fresenius Continuous Autotransfusion System Plus (CATS*plus), and the Fresenius Continuous Autotransfusion System Smart (CATSmart) were evaluated based on the mechanical processes of each device, hematocrit value of the salvaged packed red cell product, time of processing, and the advantageous accessories with each device.

Methods: Each of the autotransfusion devices were used to collect salvageable blood from the surgical field as well as to process residual blood from the cardiopulmonary bypass circuit after decannulation. The cell salvage process was performed in accordance with the manufacturer's instructions for use and the recommended settings for processing and washing. The Sorin Xtra device had the 55 mL bowl set up for all cases, while the Fresenius continuous autotransfusion systems utilized the standard disposable for each device.

Results: Each cell salvage device was employed during 30 pediatric cardiac surgery procedures, and data for each device, was broken down into four groups based on patient weight (0-10, 10-20, 20-40, and >40 kg). For all patient sizes, the Sorin Xtra tended to produce the greatest volume of cell saver product (55-825 mL) as compared to the CATS*plus and CATSmart devices (7-550 mL and 0-860 mL, respectively). The Continuous Autotransfusion System Smart tended to produce the highest hematocrit product, ranging from 44 to 81%.

Discussion: Through this evaluation, it was determined the continuous autotransfusion systems provided the highest hematocrit with the lowest recovered packed red cell volume, while the Sorin Xtra packed red cell product showed to have a lower hematocrit with a larger packed red cell volume. Each device proved effective within our pediatric population.

Keywords

pediatric; cardiopulmonary bypass; autotransfusion; blood conservation; extracorporeal technology

Introduction

The pediatric cardiac surgery population is known to be susceptible to receiving homologous blood products during the intraoperative and postoperative periods.[1,2] A device that may help reduce the amount of homologous blood product given to cardiac surgical patients is the autotransfusion device.[3,4] Studies have shown that the use of an autotransfusion device can significantly reduce donor red cell and coagulant product transfusion while also providing cost savings during cardiac surgery within the pediatric population.[5–9]

There are several devices available for cell salvage and each has distinct features and advantages within a pediatric cardiac surgical practice. The three that were selected for this comparison were the Sorin Xtra® (LivaNova USA Inc, Arvada, CO), Fresenius Continuous Autotransfusion System (CATS®plus) (Fresenius Kabi AG, Hamburg, Germany) and Fresenius CATSmart® (Fresenius Kabi AG, Hamburg, Germany). Each device relies on the process of centrifugation to remove particulate matter, pharmacological agents, and all blood components excluding erythrocytes while providing a safe,

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Table 1. Differences between each Autotransfusion device design and accessories.

Device	Centrifugal system	Wash modes	Centrifugal speed	Accessory
Sorin Xtra	Bowl (55, 125, and 225 mL)	Popt (intraoperative, optimal product) Ptsd (intraoperative, 225 mL bowl setting) Pfat (intraoperative, processing high fat level) Post-op (postoperative vacuum in post-op mode)	Customizable	Internal vacuum source, automatic processing, autostart blood processing, and data management
CATS^{plus}	One-size-fits-all model	High quality, quality, low volume, and emergency	Indicative of wash mode	Continuous access to PRC product while processing
CATSmart	One-size-fits-all model	Low volume, smart wash, emergency wash	Indicative of wash mode	Continuous access to PRC product while processing, reservoir volume and Hct sensor, integrated vacuum source, data management

reliable packed red cell (PRC) product.[10,11] Differences between each device occur with its centrifugal force component, washing method, and accessories/disposables (Table 1). The application of these devices to the pediatric population can vary with each of these products due to the amount of PRC volume that can be recovered, amount of blood product required to initiate processing, mechanism of processing, levels of washing, holdup volume within the system, the hematocrit of PRC product, and the application of each system's accessories and disposables. Each autotransfusion device is described below in more detail.

Sorin Xtra

The Sorin Xtra is an autotransfusion device that utilizes a Latham bowl design to process salvaged blood from the surgical field (Figure 1). This system provides three different sized bowl options for smaller and larger patient populations (55, 125, and 225 mL). Each bowl, dependent upon size, must be filled with the designated amount of PRCs to initiate the washing cycle. Each filling and washing cycle can be customized to optimize quality, speed of processing, and washing of the autotransfusion product. The device is programmed with three pre-set programs: Popt (Optimal Intraoperative), Pstd (Standard Intraoperative), and Post-op (Postoperative). These programs differ with respect to the priming, filling, and washing speeds as well as the wash volume. Users also have the ability to create their own program(s) so that the device works in accordance to the needs of their institution. After the termination of the washing cycle, the PRC product is removed from the bowl system and sent to a collection bag. A sensor at the outlet of the bowl system determines the hematocrit of each PRC product. Clinical validation of the Sorin Xtra has shown the consistency of its hematocrit sensors and PRC product.[12,13]

Figure 1. Sorin Xtra.

Fresenius CATS^{*plus}

The CATS^{*plus} device was the original cell salvage system from Fresenius that was developed to maximize blood collection for all sized patients (Figure 2). The CATS^{*plus} is a centrifugal system that utilizes a continuous process for an autotransfusion product. The internal centrifugal system requires approximately 7 mL of PRC to fill each of the seven individual sections that make up the washing chamber. This system allows for several types of washing options (High Quality, Quality, Low Volume, and Emergency).

Figure 2. Fresenius CATSplus.

Fresenius CATSmart

The Fresenius CATSmart is the upgraded version of the CATS*plus system (Figure 3). Processing for autotransfusion volume can be automatically initiated by the auto-start function which is activated by the weight in this device's reservoir and the reservoir volume is then brought into the centrifugal system. The internal mechanics of this device are very similar to the CATS*plus system, and also include hematocrit sensors, a smart wash feature, updated data management, and improved optics for CS processing. Similar to the Fresenius CATS*plus, the internal centrifugal system requires approximately 7 mL PRCs to fill each of the seven individual sections that makeup the washing chamber. This system provides three washing programs (Smart, Low Volume, and Emergency). In their comparison of the CATS*plus and CATSmart systems, Alberts et al.[14] validated that each system functions similarly and the hematocrit values of the end products are comparable between the two devices.

Figure 3. Fresenius CATSmart.

With respect to the technological age of each system, the Sorin Xtra is a newer autotransfusion device that has been on the market for the past couple years, while the CATS*plus system has been available for several decades and the CATSmart system is the recent upgrade of its predecessor. With the introduction of the 55 mL bowl by Sorin and the advancement of the Fresenius CATSmart, their use in the pediatric population may be more effective. Therefore, the purpose of evaluating the Sorin Xtra, CATS*plus and CATSmart devices was to determine their effectiveness in the pediatric population. A prospective clinical evaluation was performed utilizing these three autotransfusion devices. The goal for this project was to compare these devices for use in the pediatric patient population during their cardiac surgical procedures. The variables that were investigated included: the mechanical processes of each device, volume of PRC product, hematocrit value of the salvaged product (when possible), time of processing and the advantageous accessories/disposables of each device.

Methods

Each of the autotransfusion devices was used to collect salvageable blood from the surgical field and to process residual blood from the CPB circuit in a total of 90 patients, 30 cases with each system. Modified ultrafiltration (MUF) was performed on all patients less than

40 kg. After decannulation, the residual volume in the CPB circuit was transferred to the autotransfusion device and the circuit was flushed with 1,000 mL of Plasmalyte A solution (Baxter Healthcare, Dearfield, IL) in order to maximize the processing of the residual blood. Methods used for processing and washing salvaged blood followed manufacturer-recommended settings, specifically for pediatric patients. Processing and wash settings for each device are described below.

Sorin Xtra

All blood processing, regardless of patient size, was performed using the 55 mL bowl set. The 55 mL bowl was selected in an effort to get a full bowl for each patient. The bowl was processed in the Pstd mode, being filled at a speed of 300 mL/minute and washed using 300 mL of normal saline per bowl.

Fresenius CATS^{*plus}

The standard CATS^{*plus} processing kit was utilized for each case. Low Volume Wash was designated for children weighing less than 20 kg and High Quality Wash was selected for patients weighing greater than 20 kg. Low Volume Wash was used to maximize the amount of product for smaller patients, while High Quality Wash was used to optimize the product when process volume was not a concern.

Fresenius CATSmart

The CATSmart processing kit with the internal hematocrit sensor was utilized for each case. Low Volume Wash was most frequently used for patients weighing less than 20 kg. The Smart wash program was utilized for all patients weighing greater than 20 kg.

Results

Each cell salvage device was utilized on 30 cardiac surgery procedures and data for each device was broken down into four groups based on patient weight (0-10, 10-20, 20-40, and >40 kg). Of the 90 cases in which cell salvage was utilized, 88 (97.8%) produced sufficient PRC volume that could be given to the anesthesiologist post-CPB. The two cases that did not provide sufficient volume included a 5.8-kg patient with the CATSmart device that did not produce any PRC product and an 11.3-kg patient with the CATS^{*plus} device that produced 7 mL of PRC product.

Patients in the Sorin Xtra group ranged from 3.2 to 74 kg, and sufficient volume was produced for every patient. The median hematocrit of the final product was inconsistent over the four weight ranges, ranging from 20 to 58% as measured by the device's internal hematocrit sensor (Table 2). With the use of the Fresenius CATS^{*plus}, patients ranged from 2.3 to 80 kg, and adequate volume was recovered in all but one patient (Table 3). PRC product hematocrit values were not available with this system based on the device's lack of a hematocrit sensor. Data from the use of the Fresenius CATSmart is presented in Table 4. Patients ranged from 3.2 to 83 kg, and like the CATS^{*plus} device, sufficient volume was produced in all but one patient. Overall, the median hematocrit values of the end product were quite high, ranging from 44 to 81%. Both devices recovered volume and hematocrit increased as patient weight increased. A comparison of PRC volume and hematocrit of the CATSmart and Sorin XTRA is shown in Figure 4.

Table 2. Amount (mL) and hematocrit (%) of red cell product produced with the use of the Sorin Xtra. Data are presented as median (range).

Weight range (kg)	n	PRC volume	Hematocrit
0-10	14	79.5 (62-238)	45.5 (33-58)
10-20	10	71 (55-130)	40 (20-51)
20-40	1	424 (na)	39 (na)
>40	5	297 (275-820)	44 (38-47)

PRC: packed red cell.

Table 3. Amount of red cell product (mL) produced with use of the Fresenius CATS^{plus}. Data are presented as median (range).

Weight range (kg)	n	PRC volume
0-10	9	70 (18-77)
10-20	9	57 (7-86)
20-40	5	92 (84-107)
>40	7	291 (128-550)

PRC: packed red cell.

Table 4. Amount (mL) and hematocrit (%) of red cell product produced with the hematocrit sensor of the Fresenius CATSmart. Data is presented as the median (range).

Weight range (kg)	n	PRC volume	Hematocrit
0-10	12	49 (0-71)	66 (50-78)
10-20	8	63.5 (45-224)	70 (44-81)
20-40	3	124 (96-150)	76 (74-81)
>40	7	278 (77-860)	77 (68-81)

PRC: packed red cell.

Discussion

The pediatric perfusion community has utilized autotransfusion devices for many years to reduce the amount

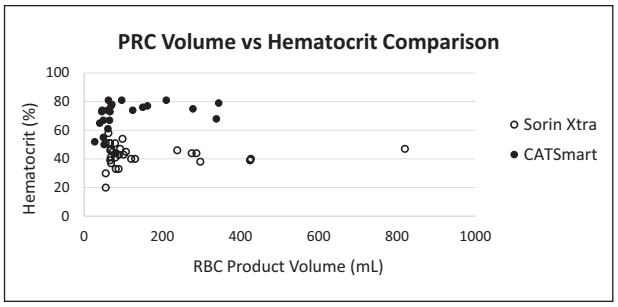

Figure 4. Comparison of Sorin Xtra and CATSmart with respect of quality and quantity of PRC product.

of exposure to homologous blood products during cardiac surgical procedures. Nathan et al.[7] demonstrated cell salvage was a tool that significantly decreased perioperative blood usage at their specific center. Further examination of PRC product was performed by Cholette et al.,[9] which showed PRC product is a safe blood product to transfuse 24 hours post collection. With the results of these studies and several others, the concept of maximizing autologous PRC product seems warranted in the pediatric cardiac surgery population.

The Sorin Xtra, CATS*plus, and CATSmart systems have different operating mechanisms and washing methods, meaning the end PRC product can vary in quality and volume. Along with the differences in processing, the internal design structure of the Sorin Xtra and the Fresenius systems differs, which plays a major role in holdup of PRC product within the device.

It has been shown that there are minimal differences in autotransfusion processing and product when comparing the CATS*plus and CATSmart.[14] A limiting factor for maximizing PRC product was noticed with the CATS systems. The design for the centrifugal system requires 7 mL of red blood cells (RBCs) to fill each of the seven internal chambers. This requires 49 mL of RBC to be held up in the centrifugal compartment before any PRC product can be produced, which is a considerable amount of holdup for pediatric patients. There are strategies to remove this volume, but the end PRC product can be diluted with these maneuvers.

The Sorin Xtra 55 mL bowl had increased processing time periods due to larger CPB circuit perfusate volumes for patients weighing greater than 13 kg; therefore, a larger bowl for this patient group would be ideal. A point of variability was noticed during processing PRC product with the Sorin Xtra 55 mL bowl. There were instances when a 55 mL bowl could not be filled, which would enact the process to concentrate the previously washed PRC product to complete the filling of the bowl to ensure a washing cycle. On occasion, a fully washed PRC product from a previous bowl would not enable a partially filled bowl to be completely filled. This scenario would result in the partially filled bowl needing to be double washed (due to the manufacturer's guidelines of washing a partial bowl). This occurrence would lead to a longer processing time and a delay in providing the PRC product to the Anesthesiologist.

Table 5. Optimal Settings for the Pediatric Patient.

Device	Wash Program	Wash Speed	Wash Volume
Sorin Xtra	Pstd	55 mL: 300 mL/min fill speed, 100 mL/min wash speed, 150 mL/min empty speed	55 mL: 300 mL
CATS*plus*	Low volume	Set speed with wash program	Dependent upon reservoir volume
CATSmart	Low volume	Set speed with wash program	Dependent upon reservoir volume

The Sorin Xtra system provides several advantages when compared to the CATS systems. This device provides multiple options for the size of a bowl, speed of wash time, wash volume, and quality of product. There is an advantage to having variable options for wash time and volume with each bowl size, but determining the optimal setting of each variable can be challenging with the pediatric population. The variability of options led to an investigation into determining the proper wash speed and bowl size for each patient. The manufacturers' suggested settings for all three systems in the pediatric setting are shown in Table 5.

Conclusion

All three devices were proven effective in the pediatric setting by providing a PRC product for patients in all weight ranges. Through this evaluation, it was determined the CATS systems provided the higher hematocrit product with the lowest recovered volume, while the Sorin Xtra produced a larger PRC volume, but with lower hematocrits. Regardless of the particular device that a practice employs, the benefits of utilizing an autotransfusion device within a pediatric cardiac surgical practice is of great value.

Limitations

There are limitations in this evaluation due to lab measurements and clinical factors. Each patient weighing less than 40 kg received MUF post CPB, which lead to a more dilute perfusate product during the autotransfusion processing time period. The hematocrit of the PRC product could not be validated by our point-of-care testing due to their inability to process a non-whole

blood product. Finally, the small number of patients did not allow for further statistical analysis on the data from the different devices.

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References

1. Durandy Y. Perfusionist strategies for blood conservation in pediatric cardiac surgery. *World J Cardiol* 2010; 2: 27–33.
2. Goel R, Cushing MM, Tobian AA. Pediatric patient blood management programs: not just transfusing little adults. *Transfus Med Rev* 2016; 30: 235–241.
3. De Somer F, Bernolet H, Bouchez S, et al. Quality evaluation of the emergency program of three contemporary cell-washing machines. *Perfusion* 2019; 34: 318–322.
4. Golab HD, Scohy TV, de Jong PL, et al. Intraoperative cell salvage in infants undergoing elective cardiac surgery: a prospective trial. *Eur J Cardiothorac Surg* 2008; 34: 354–359.
5. Karimi M, Florentino-Pineda I, Weatherred T, et al. Blood conservation operations in pediatric cardiac patients: a paradigm shift of blood use. *Ann Thorac Surg* 2013; 95: 962–967.
6. Singh SP. Strategies for blood conservation in pediatric cardiac surgery. *Ann Card Anaesth* 2016; 19: 705–716.
7. Nathan M, Tishler B, Gauvreau K, et al. A red cell preservation strategy reduces postoperative transfusions in pediatric heart surgery patients. *Paediatr Anaesth* 2018; 28: 450–457.
8. Samnaliev M, Tran CM, Sloan SR, et al. Economic evaluation of cell salvage in pediatric surgery. *Paediatr Anaesth* 2013; 23: 1027–1034.
9. Cholette JM, Powers KS, Alfieris GM, et al. Transfusion of cell saver salvaged blood in neonates and infants undergoing open heart significantly reduces RBC and coagulant product transfusions and donor exposures: results of a prospective, randomized, clinical trial. *Pediatr Crit Care Med* 2013; 14: 137–147.
10. Carless PA, Henry DA, Moxey AJ, et al. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2010; 4: CD001888.
11. Ye L, Lin R, Fan Y, et al. Effects of circuit residual volume salvage reinfusion on the postoperative clinical outcome for pediatric patients undergoing cardiac surgery. *Pediatr Cardiol* 2013; 34: 1088–1093.
12. Ovrdevest EP, Lanen PWJ, Feron JCM, et al. Clinical evaluation of the Sorin Xtra® autotransfusion system. *Perfusion* 2012; 27: 278–283.
13. Seyfried TF, Gruber M, Streithoff F, et al. The impact of bowl size, program setup, and blood hematocrit on the performance of a discontinuous autotransfusion system. *Transfusion* 2017; 57: 589–598.
14. Alberts M, Groom RC, Walczak R Jr, et al. In vitro evaluation of the Fresenius Kabi CATSmart autotransfusion system. *J Extra Corpor Technol* 2017; 49: 107–111.

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Will high-dose heparin affect blood loss and inflammatory response in patients undergoing cardiopulmonary bypass?

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Abstract

Introduction: We performed a randomized study to investigate if a high versus a standard dose of heparin dose during cardiopulmonary bypass could affect intra- and post-operative bleeding and reduce the inflammatory response.

Methods: A total of 30 patients undergoing elective coronary artery bypass grafting were randomized into high or standard dose of heparin during cardiopulmonary bypass. Blood loss was documented peri- and post-operatively, and interleukin-6, tumor necrosis factor-α, and C3 were measured in conjunction with cardiopulmonary bypass.

Results: Data from 29 patients were analyzed after exclusion of one patient. The mean initial bolus and total heparin doses were 43,000 $\pm$ 5,800 IU versus 35,000 $\pm$ 4,100 IU, ($p < 0.001$), and 58,000 $\pm$ 9,500 IU versus 45,000 $\pm$ 7,900 IU, ($p < 0.001$) in the intervention and the control group, respectively. The median intra-operative bleeding was 150 mL (interquartile range 100-325) in the control versus 225 mL (IQR 200-350) in the intervention group, $p = 0.15$. The median chest tube blood loss 12 hour post-operatively was 300 mL (interquartile range 250-385) in the control versus 450 mL (IQR 315-505) in the intervention group, $p = 0.029$. There was no significant difference between the control group and the intervention group during cardiopulmonary bypass for the measured inflammatory markers interleukin-6 ($p = 0.98$), tumor necrosis factor-α ($p = 0.72$), or C3 ($p = 0.13$).

Conclusion: This small study showed a small increase of post-operative bleeding associated with higher heparin dosage in conjunction with cardiopulmonary bypass but did not demonstrate an effect of heparin on the inflammatory response to cardiopulmonary bypass.

Keywords

cardiac surgery; cardiopulmonary bypass; heparin; inflammation; coagulation; systemic inflammatory response syndrome

Introduction

Cardiac surgery with the use of cardiopulmonary bypass (CPB) provokes the inflammatory system and induces a systemic reaction, systemic inflammatory response syndrome (SIRS). This is thought to be triggered by the artificial surface of the CPB circuit but also the cardiotomy suction, endotoxemia, ischemia-reperfusion injury and the surgical trauma itself.[1–4] A complex sequence of events, mediated by different agents of the immune system, leads to a final activation of leukocytes and endothelial cells that are responsible for cell dysfunction in different organs.[2]

The complement system is an immunologic mechanism in the inflammatory process and is activated by CPB. Its functions include mediating inflammation, opsonisation of antigenic particles, and causing membrane damage to pathogens, via the membrane attack complex.[5,6] Complement activation is associated with inflammatory injury in a heterogeneous group of clinical settings including cardiac surgery. Multiple pathways are responsible for complement activation in cardiac surgery including bio incompatibility of the CPB circuit, reversal of heparinization, and activation via tissue ischemia and reperfusion.[5] When blood moves through the CPB circuit, which lacks natural occurring endothelium, the complement system and its alternative

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pathway is provoked, resulting in an anaphylactic and chemotactic activity.[1]

This systemic inflammatory process can result in organ dysfunction, such as lung injury, renal failure, myocardial dysfunction, bleeding disorders, and generalized profound vasodilation,[1,2,4,7] thus increasing postoperative morbidity and mortality.[4,7]

Heparin administration for CPB, historically, has been based on a standard, weight-based initial dose ranging from 200 to 400 IU (International Units)/kg with intermittent maintenance with bolus dosing along with heparin priming of the circuit to further minimize the risk of circuit thrombosis. These standards were instituted and widely followed until the 1960s, when Hattersley developed the activated clotting time (ACT), which revolutionized heparin monitoring.[6,8–10]

Several studies suggest that heparin apart from being an anticoagulant also possesses various anti-inflammatory effects,[2,11–13] which could benefit patients undergoing heart surgery.

The aim of this study was to investigate in a randomized study if a high dose of heparin versus a standard dose during CPB could affect intra- and post-operative blood loss and reduce inflammatory response.

Methods

Selection criteria and randomization

This randomized trial was approved by the regional Human Research Ethics Committee (Stockholm, Sweden, 2017/1344-31/1), with 30 patients planned to be included. After receiving written information and signing consent, a closed envelope regime was used to randomize patients into either the control group or the intervention group. All patients included were scheduled for elective coronary artery bypass grafting (CABG) surgery with the use of normothermic CPB due to cardiovascular disease at Karolinska University Hospital, Stockholm. The following exclusion criteria were applied: Former heparin-induced thrombocytopenia, known pre-existing hemolytic disorders, known coagulation system disorders, chronic inflammatory disease, and ongoing anticoagulant treatment other than acetylsalicylic acid (ASA).

Intra-operative procedure

Anesthesia was induced using fentanyl and propofol, in some cases with additional midazolam. Intubation was facilitated with atracurium. Patients were ventilated to achieve normocapnia. Anesthesia was maintained with intermittent fentanyl and sevoflurane before CPB and with an infusion of propofol during and after CPB. All patients were given 2 g tranexamic acid before the surgery commenced, followed by an infusion of 5 mg/kg/h during the operation according to a local standard.

Cardiopulmonary system

A heart-lung machine (Stöckert S5) with an open CPB system was used. The CPB circuit consisted of an Inspire HVR reservoir (LivaNova) and the Inspire 8F oxygenator (LivaNova), together with the RevOlution centrifugal pump (LivaNova). After initial 3-5 minutes of flushing the dry circuit with carbon dioxide, priming consisted of Ringer acetate 1,100-1,300 mL, mannitol 250-300 mL, and 7,500 IU of heparin. Heparin was then administered intravenously to the patient according to protocol before initiation of and during CPB. Normothermia (34-37°C) were maintained during the operation. Cardiac arrest was induced and maintained with cold blood cardioplegia. Two machine suckers were used and reinfused in the integrated cardiotomy reservoir. After weaning of CPB and decannulation, the remaining blood in the CPB circuit was re-transfused directly to the patient using an empty Ringer acetate-bag.

ACT measurement

ACT was measured before and during CPB with high range ACT kaolin cartridges (Medtronic ACT Plus® System).[14] Blood sampling was drawn from the patients' arterial line or from the CPB circuit. After weaning of bypass and protamine reversal, a high-range heparinase test cartridge (Medtronic ACT Plus System) was used in addition to ACT to determine any residual heparin in the blood.

HeProCalc

Based on patient data (sex, age, body surface area, and baseline ACT) and the setup of the CPB circuit (prime volume and heparin content), the initial heparin dose was calculated with a computer application (HeProCalc) and its empirically produced algorithm. All ACT values measured during CPB are continuously inserted in the application as well as additional heparin doses and the temperature of the arterial line of the CPB circuit. Based on calculated heparin response and consumption, HeProCalc calculates a real-time heparin concentration (IU of heparin/kg) and also a heparin response index to discover the potential need for antithrombin III. Additional doses of heparin are suggested by the application when necessary. Upon weaning of CPB, a suggested dose of protamine to eliminate remaining heparin in the circuit is presented, based on all ACT values, total amount of heparin given and heparin consumption over time.[15]

Data collection and blood sampling

Prior to surgery; sex, body surface area (BSA), weight, creatinine, platelet count, hemoglobin value, and prothrombin complex values from the patient's medical notes were put on record. Intra-operatively, the total amount of heparin, protamine, and ACT values were recorded, as well as time of surgery, CPB and the duration of the aortic cross-clamp. The peri-operative blood loss and fluid balance was also documented. These data were estimated according to clinical routine. The post-operative blood loss was documented from the chest tubes 12 hours after weaning of CPB.

Pro-inflammatory markers

To measure inflammatory response and complement activation markers interleukin (IL)-6, tumor necrosis factor (TNF)-α and C3 were analyzed, according to Karolinska University Laboratory standard protocol. Except baseline value before CPB (T_0), blood was collected 3 minutes after the initial heparin bolus given prior initiation of CPB (T_1), 15 minutes after initiation of CPB (T_2), 5 minutes after declamping the aortic cross-clamp (T_3), 3 minutes after protamine administration (T_4), and 3 hours after weaning of bypass (T_5).

The control group and the intervention group

In the control group, standard protocol based on HeProCalcs recommendations were used for anticoagulation before and during CPB. Patients in this group received an initial bolus of heparin to reach an ACT of 480 seconds before going on CPB. ACT and the calculated heparin concentration were then kept at minimum of 480 seconds and 250 IU/kg during CPB. If the ACT level or the calculated heparin concentration was below these levels, 2,500 IU of heparin were administered to the CPB circuit by the perfusionist.

In the intervention group, HeProCalcs recommendations were used for anticoagulation before and during CPB. Patients in this group received an increased initial bolus of heparin to reach an ACT of 680 seconds before going on CPB. ACT and the calculated heparin concentration were then kept at minimum of 680 seconds and 550 IU/kg during CPB. If the ACT level or the calculated heparin concentration was below these levels, 2,500 IU of heparin were administered to the CPB circuit by the perfusionist.

HeProCalc was used to determine the amount of protamine needed to reverse remaining heparin after weaning of CPB in both groups.

The administration of antithrombin III was not specified in the study protocol and was given at the discretion of the anesthesiologist according to local routine at our department. Generally 500 IU of antithrombin III was given if the ACT was too low in relation to the calculated heparin concentration and additional heparin did not have the desirable effect. HeProCalc was used as a guidance to assess the need of antithrombin III in both groups.

Statistical analysis

Assuming a statistical power of 80% to reach an alpha level of 5%, the needed sizing of each group would be 15 patients to discover a difference of 300 mL in blood loss between groups, considered to be a clinically significant difference. Previous studies[2,14] have shown that assuming a blood loss variability of 300 mL is reasonable. R (Version 3.5.2) was used to analyze collected data. Mann–Whitney U-test and Student's t-test was used for numerical variables depending on normal distribution. For categorical variables Fishers exact t-test was used. For pro-inflammatory markers, the total area under the curve for each group was compared using Mann–Whitney U-test.

Results

Data from 30 patients were collected from 23 November 2017 to 30 October 2018. Results from 29 patients were analyzed after one patient was excluded. The excluded patient presented high inflammation markers after surgery, and when reviewing the patient chart, it was previously stated that the patient had been diagnosed with a chronic inflammatory disease. The control group contained 15 patients and the intervention group 14 patients.

Baseline characteristics

Baseline characteristics are presented in Table 1. Of the 29 included patients, 26 were men. Apart from the pre-operative serum creatinine levels (mean ± standard deviation (SD)) being somewhat higher in the intervention group compared to the control group, 94 ± 18.9 μmol/L versus 80 ± 10.8 μmol/L, $p = 0.02$, there were no other statistically significant differences between the groups in other baseline parameters such as age, sex, weight, BSA, pre-operative hemoglobin levels, platelet count, international normalized ratio (INR) or ACT.

Heparin and protamine

Table 2 shows intra- and post-operative data. In the intervention group, a higher heparin dose (mean ± SD) was administered as compared to the control group before

initiating CPB and in total for the entire duration of CPB, (43,000 ± 5,800 IU vs 35,000 ± 4,100 IU, $p < 0.001$, respectively, 58,000 ± 9,500 IU vs 45,000 ± 7,900 IU, $p < 0.001$). The intervention group received a higher dose (mean ± SD) of protamine after CPB to reverse heparin as compared to the control group (321 ± 47 mg vs 228 ± 36 mg, $p < 0.001$). Two patients in the control group and one patient in the intervention group had the need for antithrombin III in conjunction with CPB to reach desired levels of ACT and heparin concentration.

Blood loss

The median intra-operative blood loss was 150 mL (IQR 100-325) in the control group versus 225 mL (IQR 150-500) in the intervention group, $p = 0.15$. The median values for post-operative blood loss 12 hours after weaning of CPB were 300 mL (IQR 250-385) in the control group and 450 mL (IQR 315-505) in the intervention group, $p = 0.029$ (Figure 1).

Table 1. Baseline characteristics (n or mean ± SD).

	Control group	Intervention group	p value
Number of patients	15	14	
Age, years	69 ± 6.8	68 ± 9.0	0.80
Sex, male	13	13	1
Weight, kg	87 ± 15.4	79 ± 15.2	0.20
BSA, m^2	2.03 ± 0.18	1.94 ± 0.21	0.23
Creatinine, µmol/L	80 ± 10.8	94 ± 18.9	0.02
Hemoglobin, g/L	141 ± 11.3	142 ± 9.2	0.71
Platelet count, $\times 10^9$	202 ± 52.8	225 ± 46.1	0.23
INR	1.05 ± 0.07	1.02 ± 0.09	0.42
Initial ACT, seconds	137 ± 12.9	131 ± 9.5	0.09

SD: standard deviation; BSA: body surface area; INR: international normalized ratio; ACT: activated clotting time.

Pro-inflammatory markers

IL-6. Figure 2 shows IL-6 levels using boxplots for each group over time. There was no significant difference between the control group and the intervention group within T_0 to T_5 ($p = 0.98$).

TNF-α. Over time, the median TNF-α levels increased in both groups (Figure 3), reaching their peak at T_5. No statistically significant difference could be found between the control group and the intervention group within T_0 to T_5 ($p = 0.72$).

C3. Following baseline values, C3 levels decreased after the initial heparin bolus and reached the lowest values for both groups 15 minutes after initiating CPB (T_2) as shown in Figure 4. Observing T_3 to T_5 the values seemed to return toward baseline values; however, with observed higher levels of C3 in the control group as compared to the intervention group ($p = 0.13$).

Discussion

In this study, we aimed to test if a higher dose of heparin before and during CPB compared to a standard dose could benefit patients undergoing on-pump CABG, regarding blood loss and inflammatory response associated with this kind of surgery, since heparin has showed itself to possess anti-inflammatory characteristics.[2,11–13]

Does a higher heparin dose during CPB affect blood loss?

Current targets for anticoagulation during CPB remain largely centered around the early work of Bull and colleagues, who investigated protocols for heparinization

Table 2. Intra- and post-operative data (n or mean ± SD).

	Control group	Intervention group	p value
Number of patients	15	14	
Initial heparin dose prior to CPB, IU	35,000 ± 4,100	43,000 ± 5,800	<0.001
Duration of surgery, minute	195 ± 43	179 ± 42	0.30
CPB time, minute	72 ± 19	70 ± 19	0.76
Cross-clamp time, minute	54 ± 15	50 ± 17	0.49
Total amount of heparin, IU	45,000 ± 7,900	58,000 ± 9,500	<0.001
Patients given AT III	2	1	1
Total amount of protamine, mg	228 ± 36	321 ± 47	<0.001
ACT after heparin neutralization, seconds	123 ± 7	125 ± 6	0.39
Peri-operative fluid balance, mL	2,090 ± 846	2,300 ± 814	0.48

SD: standard deviation; CPB: cardiopulmonary bypass; IU: international units; AT III: antithrombin III; ACT: activated clotting time.

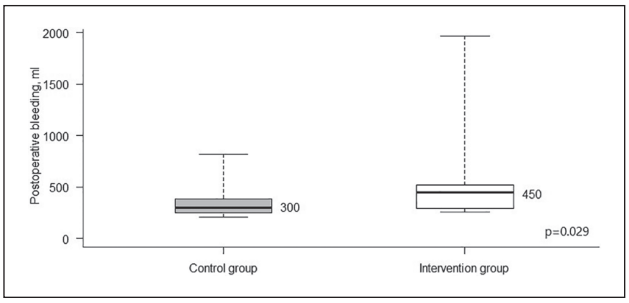

Figure 1. Post-operative blood loss (mL) using boxplots (median with IQR (interquartile range) and range).

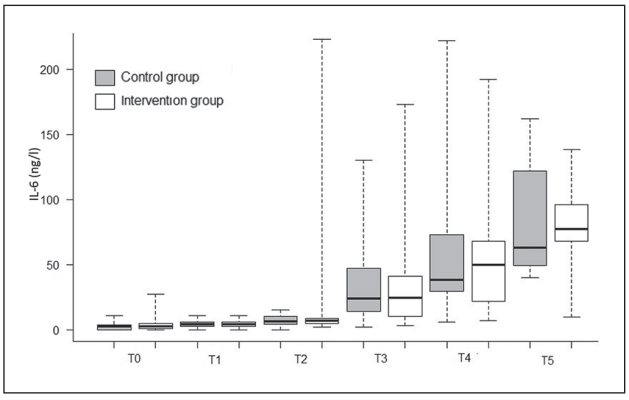

Figure 2. IL-6 from T_0 to T_5 described using boxplots for each group (median with IQR (interquartile range) and range).

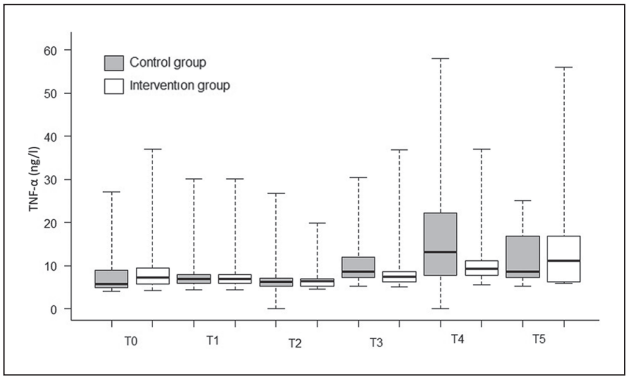

Figure 3. TNF-α from T_0 to T_5 described using boxplots for each group (Median with IQR (interquartile range) and range).

using ACT. Their work was based on the recognition that patients would often have variability in heparin dose response and heparin metabolism despite similar ACT values. These studies were the foundation for the adoption of an ACT of at least 480 seconds during CPB. Since that time, there has been considerable inter-institution variability. While some institutions still require an ACT of 480 seconds, others have adopted modified ACT values of 400 seconds or even

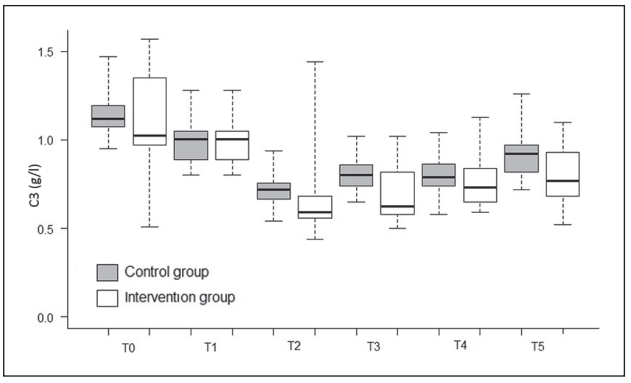

Figure 4. C3 from T_0 to T_5 described using boxplots for each group (Median with IQR (interquartile range) and range).

300 seconds.[9] According to Bull, an upper limit of 600 seconds should not be exceeded[9] while, for example, Palmer et al.[8] has shown that an average ACT between 500-700 seconds during CPB is associated with significant lesser blood loss.

Both intra- and post-operatively, there are tendencies of more blood loss in the intervention group compared with the control group, with a median difference of 75 mL ($p = 0.15$) respectively 150 mL ($p = 0.029$). Additional blood loss of 75 mL in conjunction with surgery, respectively, 150 mL post-operatively could prove to be clinically significant in some patients but should not cause great concern generally or require blood transfusion.

In the study by Paparella et al.,[2] the high heparin group (600 IU/kg) had less activation of the coagulation during CPB and thus maintained coagulation post CPB, which should mean that the post-operative blood loss in that group would be reduced compared to the control group.

On the contrary in our study, we have found a significant difference between the groups with increased blood loss post-operatively in patients who had been given more heparin. These findings are also in contrast with previous studies.[8]

The results also show that the intervention group got more protamine then the control group. While protamine primarily neutralizes heparin, it also possesses anticoagulant properties which are attributed to interaction with platelet function, interference with coagulation factors, and potentiating clot lysis.[16] Available evidence[16–18] suggests not exceeding a protamine to heparin ratio of 1:1 to reduce post-operative bleeding and transfusion requirements. Based on this ratio, protamine is administered such that 1 mg of protamine is administered per 100 U of heparin. However, looking back on the results of this study, no patient in either group received a protamine dose exceeding a protamine to heparin ratio of 1:1 even if the total dose of protamine differed between the two groups. ACT after protamine

administration did also not differ between the groups (Table 2).

One patient in the intervention group was re-operated due to excessive bleeding (1,970 mL 12 hour after weaning from CPB). ACT was normal at that time and a surgical bleeding source was found when re-exploring the patient. Thus, residual heparin in this patient as a main cause for the excessive blood loss seems less likely even though this patients' blood loss could have been a confounding factor to the results.

Inflammatory response in patients undergoing CPB and potential relation to heparin

Heparin-coated circuits have been shown to reduce cytokine production and complement activation,[13] and there are studies showing that heparin itself could reduce complementary response by regulating steps in its different pathways.[11] However, the effect of a higher kept heparin concentration during the duration of CPB has not been evaluated regarding its ability to reduce the inflammatory response in heart surgery.

IL-6, TNF-α, and C3 are previously studied inflammatory markers in heart surgery.[1,2,4] In this study, cytokines IL-6 and TNF-α increases over time in patients undergoing CPB and are not returning to baseline values during the observed period. C3, an end-phase protein of the complement system, decreases over time in both groups. This finding is in contrast with other studies that show increased complement activation during CPB.[11–13] The decrease in our study might be attributed to the dilution of priming solution of the CPB circuit, which we have not compensated for.

Paparella et al.[2] studied the impact of two different heparin doses in patients undergoing elective CABG requiring CPB, regarding inflammatory response and preservation of the coagulation system. They concluded that an initial heparin dose of 600 IU/kg before initiating CPB was associated with less platelet activation and less thrombin formation compared to an initial heparin dose of 300 IU/kg. However, the impact of a higher heparin dose on pro-inflammatory cytokine IL-6 and TNF-α release was minor and insignificant in that study.

In our setting, we aimed to keep a higher heparin concentration during CPB in addition to the higher bolus dose of heparin in the intervention group, but no statistically significant differences could be found between the different inflammatory markers within the studied period, as compared to the control group.

In this study, we only choose to monitor the evolution of IL-6, TNF-α, and C3. SIRS caused by CPB is a multifaceted mechanism in which several mediators are involved in an advanced interplay. Other pro-inflammatory cytokines and markers or adhesion- and complement molecules maybe would have progressed and reacted to different heparin doses in another way.

Limitations

An important limitation of this study was the small sample size. We did not have information describing the total use of tranexamic acid in each patient in this study. There was also a statistically significant difference between the groups regarding pre-operative creatinine levels that was not accounted for. All patients in this study went through CABG procedures and relatively short CPB times, and this intervention might have shown greater impact on both inflammatory markers and blood loss in more advanced surgery requiring extended durations of CPB. Another limitation of the study was that we did not have information about pre-operative platelet function, the number of grafts being used and vessel harvesting technique used, which could possibly affect blood loss.

Conclusion

This small study showed a small increase of post-operative bleeding associated with higher heparin dosage in conjunction with CPB but did not demonstrate an effect of heparin on the inflammatory response to CPB.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P Srisophon-Stensved, founder of computer application HeProCalc, is employed as a perfusionist at the same institution as the authors and was consulted when planning the project how to dose heparin to reach the different ACT and heparin levels in the two studied groups. He has not had any other involvement in this project.

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References

1. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. *Eur J Cardiothorac Surg* 2002; 21: 232–244.
2. Paparella D, Al Radi OO, Meng QH, et al. The effects of high-dose heparin on inflammatory and coagulation parameters following cardiopulmonary bypass. *Blood Coagul Fibrinolysis* 2005; 16: 323–328.

3. Landis C. Pharmacologic strategies for combating the inflammatory response. *J Extra Corpor Technol* 2007; 39: 291–295.
4. Kraft F, Schmidt C, Van Aken H, et al. Inflammatory response and extracorporeal circulation. *Best Pract Res Clin Anaesthesiol* 2015; 29: 113–123.
5. Stahl GL, Shernan SK, Smith PK, et al. Complement activation and cardiac surgery: a novel target for improving outcomes. *Anesth Analg* 2012; 115: 759–771.
6. Gravlee GP. *Cardiopulmonary bypass and mechanical support: principles and practice*. 4th ed. Philadelphia, PA: Wolters Kluwer Health, 2016.
7. Nee L, Giorgi R, Garibaldi V, et al. Ischemia-modified albumin and adenosine plasma concentrations are associated with severe systemic inflammatory response syndrome after cardiopulmonary bypass. *J Crit Care* 2013; 28: 747–755.
8. Palmer K, Ridgway T, Al-Rawi O, et al. Heparin therapy during extracorporeal circulation: deriving an optimal activated clotting time during cardiopulmonary bypass for isolated coronary artery bypass grafting. *J Extra Corpor Technol* 2012; 44: 145–150.
9. Lander H, Zammert M, FitzGerald D. Anticoagulation management during cross-clamping and bypass. *Best Pract Res Clin Anaesthesiol* 2016; 30: 359–370.
10. Shore-Lesserson L, Baker RA, Ferraris VA, et al. The society of thoracic surgeons, the society of cardiovascular anesthesiologists, and the American society of extracorporeal technology: clinical practice guidelines-anticoagulation during cardiopulmonary bypass. *Ann Thorac Surg* 2018; 105: 650–662.
11. Edens E, Lindhardt RJ, Weiler JM. Heparin is not just an anticoagulant anymore: six and one-half decades of studies on the ability of heparin to regulate complement activity. *Compl Prof* 1993; 1: 96–120.
12. Mousavi S, Moradi M, Khorshidahmad T, et al. Anti-inflammatory effects of heparin and its derivatives: a systematic review. *Adv Pharmacol Sci* 2015; 2015: 507151.
13. Mahmood S, Bilal H, Zaman M, et al. Is a fully heparin-bonded cardiopulmonary bypass circuit superior to a standard cardiopulmonary bypass circuit? *Interact Cardiovasc Thorac Surg* 2012; 14: 406–414.
14. Lee JM, Park EY, Kim KM, et al. Comparison of activated clotting times measured using the Hemochron Jr. Signature and Medtronic ACT Plus during cardiopulmonary bypass with acute normovolemic haemodilution. *J Int Med Res* 2018; 46: 873–882.
15. Kjellberg G, Sartipy U, Van Der Linden J, et al. An adjusted calculation model allows for reduced protamine doses without increasing blood loss in cardiac surgery. *Thorac Cardiovasc Surg* 2016; 64: 487–493.
16. Boer C, Meesters MI, Veerhoek D, et al. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. *Br J Anaesth* 2018; 120: 914–927.
17. Despotis GJ, Gravlee G, Filos K, et al. Anticoagulation monitoring during cardiac surgery—a review of current and emerging techniques. *Anesthesiology* 1999; 91: 1122–1151.
18. Kunst G, Milojevic M, Boer C, et al. 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. *Br J Anaesth* 2019; 123: 713–757.

Original Paper

Perfusion

Using a quality improvement initiative to reduce acute kidney injury during on-pump coronary artery bypass grafting

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Abstract

Introduction: In response to a perceived high incidence of acute kidney injury following cardiopulmonary bypass at our institution, a quality improvement initiative consisting of a systematic change to a delivered oxygen (DO_2) goal-directed perfusion practice was implemented. We sought to maintain $DO_2 > 270\,mL/min/m^2$ to reduce the incidence of acute kidney injury.

Methods: `The study population included all patients receiving isolated, non-emergent, on-pump coronary artery bypass grafting from January 2015 through December 2018, excluding patients requiring preoperative hemodialysis. DO_2 goal-directed perfusion was instituted in February 2017. Acute kidney injury was defined using Acute Kidney Injury Network criteria.

Results: The pre–goal-directed perfusion cohort included 257 patients, and the post–goal-directed perfusion cohort included 226 patients. The DO_2 was significantly higher in the post–goal-directed perfusion group ($p < 0.001$). Postoperative change in serum creatinine and incidence of acute kidney injury were significantly lower in the post–goal-directed perfusion group ($p < 0.001$, $p = 0.001$, respectively). Estimation with probit and ordered probit models support these findings.

Conclusion: This initiative confirms previous assertions that DO_2 is a critical intraoperative parameter and should direct perfusion intervention accordingly.

Keywords

cardiopulmonary bypass; acute kidney injury; delivered oxygen; goal-directed perfusion; quality improvement; cardiac surgery

Introduction

Background

Acute kidney injury (AKI) following surgery utilizing cardiopulmonary bypass (CPB) is an expensive complication with high morbidity and has a reported incidence as high as 55.6%.[1] Even in relatively less complex on-pump surgeries, such as isolated coronary artery bypass grafting (CABG), AKI incidence has been found to be as high as 43.9%.[2] Even seemingly small increases in serum creatinine (SCr) constitute perioperative AKI, which is an independent risk factor for adverse outcomes including both in-hospital and long-term mortality, subsequent requirement for renal replacement therapy, increased length of hospitalization, and increased resource use.[3,4] It is estimated that incremental costs associated with AKI following cardiac operations are about US$1 billion annually.[5]

While the pathogenesis of AKI in the setting of CPB is complex and multifactorial, one well-established consideration is that during CPB, high metabolic demands in the renal medulla are not sufficiently met by delivered oxygen (DO_2) either due to excessive hemodilution or

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decreased renal blood flow leading to either or both ischemic and inflammatory injury.[6,7] DO_2 during CPB is largely determined by the hemoglobin level and pump index, and it has been shown previously that a minimum DO_2 (270-280 mL/min/m^2) below a critical threshold is a sensitive and specific predictor of perioperative AKI.[6]

Most recently, Ranucci et al.[8] published the results of an international multi-center randomized control trial wherein they evaluated the efficacy of employing DO_2 goal-directed perfusion (GDP) for management of CPB. Their results showed that by closely monitoring and modifying the patients' CPB parameters to maintain a DO_2 greater than 280 mL/min/m^2 the incidence of Acute Kidney Injury Network (AKIN) Stage 1 AKI was reduced by 11%.

Purpose

In response to a perceived high incidence of AKI following CPB by surgeons at our institution, we set out initially to identify and limit variations of our clinicians' practices from evidence-based practices. Furthermore, we sought to identify preoperative and intraoperative variables that might lead to the perceived incidence of AKI. In reviewing the literature and performing chart reviews of the perfusion records of patients who received CABG, it was hypothesized that insufficient DO_2 could be associated with an increased risk of AKI in our population.

A quality improvement (QI) initiative consisting of a systematic change to a DO_2 GDP practice was implemented in February 2017. The new procedures had a goal of reducing AKI incidence by maintaining $DO_2 > 270$ mL/min/m^2 during CPB. We expected to demonstrate that DO_2 GDP can improve perfusion practices resulting in a decreased incidence of AKI.

Methods

Study design

The University of Texas Health Science Center at San Antonio's Institutional Review Board approved this study and granted the study an exemption (HSC20170344H). The REDCap (Research Electronic Data Capture) database application was utilized to store and manage our data.[9] The chosen study population included all patients receiving isolated, non-emergent, on-pump CABG from January 2015 through December 2018 at University Hospital in San Antonio, excluding patients requiring preoperative hemodialysis. Beginning February 2017, DO_2 GDP was instituted. The study population included a post-GDP group operated on after institution of the QI initiative, compared with a pre-GDP of near equal size operated on prior to the implementation of the QI initiative.

DO_2 GDP constituted the use of intraoperative calculation of DO_2 with attempts at increasing DO_2 when calculated DO_2 fell below or near 270 mL/min/m^2; these attempts consisted, principally, of perfusionist-directed increases in pump flow, hemoconcentration, or blood transfusion as indicated. If DO_2 was found to be at or approaching the threshold, pump flow was increased as appropriate to maintain adequate DO_2. If this was not possible, due to reaching a maximum allowable pump flow as limited by obstruction of surgical field or CPB constraints, the decision to proceed to blood transfusion was discussed with the team and administered in the absence of contraindications, namely patients who declined to provide consent and those anticipated to require future solid organ transplantation who therefore had greater concern for antibody production status post transfusion.

Independent variables included perfusionist-modified on-pump hemoglobin and pump index, which in turn determined DO_2, as well as preoperative variables including hemoglobin and measures of renal function, namely SCr and estimated glomerular filtration rate (eGFR). To aid in the implementation of the QI initiative, it was necessary to provide clinicians a simple and rapid means of determining DO_2 status during CPB to allow for effective decision making. We created a tool with Microsoft Excel™ (Microsoft Corporation, Redmond, Washington, USA) that utilized the DO_2 equation to calculate DO_2 using clinician inputs of partial pressure of arterial oxygen (PaO_2), hemoglobin (Hg), saturation of arterial oxygen (SaO_2), and cardiac (pump) index (CI). Clinicians could then interpret the calculated DO_2 and modify pump settings as needed to meet DO_2 goals. Outcomes of interest were incidence of AKI, postoperative change in SCr, and mortality.

Data collection

All data were collected retrospectively from patients' electronic medical records using Allscripts Sunrise™ (Allscripts Healthcare Solutions, Inc., Chicago, Illinois, USA), Epic© (Epic Systems Corporation, Verona, Wisconsin, USA), as well as data submitted to the Society of Thoracic Surgeons National Database as a participant. Demographic data collected included gender, age, race, and ethnicity. Preoperative data collected included body mass index (BMI), hemoglobin, history of diabetes mellitus (DM), hemoglobin A_{1c} (HbA_{1c}), and SCr. Male patients with a preoperative hemoglobin less than 13.5 g/dL or female patients with a preoperative hemoglobin less than 12 g/dL were considered anemic. The CKD-Epi (Chronic Kidney Disease Epidemiology Collaboration) equation, which uses gender, age, race, and SCr (mg/dL) to determine eGFR (mL/min/1.73 m^2), was employed to determine the patient's preoperative kidney function.[10]

Intraoperative data collected included, at 30-minute intervals while on pump was SaO_2, PaO_2, and Hg, and at

$$DO_2 = CI \times (Hb \times SaO_2 \times 1.34 + PaO_2 \times 0.003)$$

Figure 1. Delivered oxygen equation (DO_2).
DO_2: delivered oxygen; CI: cardiac index; Hb: hemoglobin (g/dL); SaO_2: saturation of arterial oxygen; PaO_2: partial pressure of arterial oxygen.

15-minute intervals while on pump, CI, and mean arterial pressure (MAP). These were used to calculate DO_2 via the DO_2 equation (Figure 1).

Other intraoperative variables included pump time, prime volume, use of retrograde autologous priming (RAP), use of red blood cells (RBCs) in the CPB prime, and use of RBC transfusions.

Postoperative data collected included SCr up to discharge and 30-day mortality. SCr was recorded postoperatively at irregular intervals on the order of hours as needed clinically. To distinguish changes in SCr attributable to the operation from non-operative causes of SCr changes, we limited our observations of SCr to the 72-hour postoperative period. AKI was defined using AKIN criteria, which uses both increases in SCr and decreases in urinary output to diagnose AKI and to stratify AKI into three stages of severity.[11] Due to limitations in the precision of measuring urine volume and the limited frequency with which measurements were recorded, only SCr criteria were used to determine AKI staging. Therefore, patients experiencing either an absolute increase in SCr of 0.3 mg/dL or greater or a relative increase of 150% or greater were considered to have AKI Stage 1; patients experiencing a relative increase of 200% or greater were considered to have AKI Stage 2; patients experiencing a relative increase of 300% or greater were considered to have AKI Stage 3 (where unspecified, "AKI" refers to any case meeting criteria for AKI Stage 1, AKI Stage 2, or AKI Stage 3).

Materials

Terumo CDI-500® (Terumo Corporation, Tokyo, Japan) was used with the arterial cuvette and venous line oximeter and the iStat POC blood analyzer (Abbott Laboratories, Lake Bluff, Illinois, USA) with the CG8 blood gas and CG4 lactate cuvettes.

CPB disposable equipment used consisted of LivaNova Inspire 6S (LivaNova, PLC, London, UK) with closed reservoir, LivaNova Revolution, rollerhead pump driven hemofilter, LivaNova PHISIO external arterial line filter, Quest MPS microplegia (Quest Medical, Inc., Allen, Texas, USA), and 3/8 AV loop. The static prime of this circuit was approximately 1,200 mL. The clinician consulted the surgical team for use of a 1/2-3/8 AV loop, LivaNova Inspire 8, or Terumo FX15-40 depending on patient size.

CPB prime consisted of Plasmalyte-A (Baxter International, Inc., Deerfield, Illinois, USA), 25% albumin, heparin 10,000 IU, Amicar 5 mg or TXA (market availability dependent), 12.5 g mannitol (withheld if patient had chronic kidney disease Stage 2 or greater), and $NaHCO_3$ as indicated for base excess less than −2. Albumin level was calculated by dividing dose of albumin (grams) by total circuit volume (milliliters) and added to maintain a 3-5% level.

Perfusion techniques

At the initiation of CPB, temperature was allowed to passively decrease to 34°C. Quest MPS microplegia was administered upon cross-clamping and every 20 minutes with some variability in timing, volume, route, and use of a "hot shot" (warm blood reperfusion). Shed blood was returned to the patient using the C.A.T.S®plus Continuous Autotransfusion System (Fresenius SE & Co. KGaA, Bad Homburg, Germany).

In the pre-GDP group, initial CI was determined entirely by the clinicians' evaluation of blood pressure, mixed venous oxygen saturation, and bilateral cerebral near-infrared spectroscopy. CI was subsequently increased if acidosis occurred. Vasopressors were used to maintain MAP greater than 50 mmHg if increased flows were insufficient.

In the post-GDP group, initial CI was determined similarly. Beginning with the initial arterial blood gas measurement, CI was titrated as directed by DO_2 GDP as described previously. Although blood gas analysis was obtained at 30-minute intervals (and as a consequence, DO_2 was directly measured and recorded only at these intervals), the use of the Terumo CDI-500® allowed clinicians to monitor, interpret, and respond to data indicating the estimated DO_2.

Statistical analysis

Shapiro–Wilks tests were used to assess normality of each quantitative variable. Wilcoxon rank-sum tests and two-proportion z tests were then used to assess the statistical significance of differences between quantitative and categorical variables, respectively. A p value <0.05 was considered significant. Simple odds ratios were performed with categorical variables that were found to be statistically significantly different between the two groups to assess their contribution to AKI risk. Wilcoxon rank-sum tests were again employed to determine whether quantitative variables that were found to be statistically significantly different between the two groups contributed to their respective risks of AKI.

In an additional analysis, we used a probit model in which the dependent variable was AKI (0 = no AKI, 1 = AKI). The independent variables were DO_2 (mean on pump), anemia (0 = no anemia; 1 = anemia), eGFR, MAP (minimum on pump), and utilization of GDP (0 = pre-GDP, 1 = post-GDP). For additional analysis,

Table 1. Characteristics of the study population

Variables	Pre-GDP (n = 257)	Post-GDP (n = 226)	p value
Male gender	182 (71)	179 (79)	0.034
Age (years)	60.9 ± 9.7	60.5 ± 10.0	0.803
Hispanic ethnicity	131 (51)	139 (62)	0.020
BMI (kg/m^2)	30.7 ± 5.8	30.7 ± 5.5	0.968
Anemia	121 (47)	100 (44)	0.535
Diabetes	172 (67)	141 (62)	0.298
HbA_{1c} (%)	7.72 ± 2.10	7.43 ± 2.05	0.072
Preoperative SCr	1.01 ± 0.53	1.10 ± 0.43	<0.001
eGFR	80.9 ± 23.2	75.5 ± 23.4	0.013

GDP: goal-directed perfusion; BMI: body mass index; HbA_{1c}: glycated hemoglobin; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; SD: standard deviation.
Values are mean ± SD or n (%).

we created an ordered probit model to analyze a second dependent variable that incorporated AKI stage (0 = no AKI, 1 = AKI Stage 1, 2 = AKI Stage 2 or 3).

Results

Characteristics of the study population

The pre-GDP cohort included 257 patients, and the post-GDP cohort included 226 patients (n = 483). Table 1 summarizes the demographic and preoperative variables of the two study groups. There was no statistically significant difference between the pre-GDP and post-GDP group regarding age, BMI, prevalence of anemia or DM, or HbA_{1c}. While there were more Hispanic patients in the post-GDP group, ethnicity did not represent an independent risk factor for AKI in our sample (odds ratio (OR) = 1.01, 95% confidence interval (CI): 0.70-1.47, $p = 0.962$). Similarly, while there were more male patients in the post-GDP group, male gender did not represent an independent risk factor for AKI in our sample (OR = 0.91, 95% CI: 0.60-1.40, p = 0.677).

In addition, while the post-GDP group had statistically significant higher preoperative SCr, this difference did not represent an independent risk factor for AKI in our sample (p = 0.159). Finally, the statistically significant lower eGFR in the post-GDP group was also not an independent risk factor for AKI in our sample (p = 0.171).

Intraoperative pump variables

Variables associated with the pump that were not included in the changes made to perfusion practices via DO_2 GDP could reasonably have contributed to a difference in AKI incidence such as pump time, prime volume, and the utilization of RAP, RBCs in the prime, and packed RBC transfusions, but none of these variables were statistically significantly different between the two groups as outlined in Table 2.

Table 2. Intraoperative pump variables

Variables	Pre-GDP (n = 257)	Post-GDP (n = 226)	p value
Pump time (minutes)	96.6 ± 29.2	98.4 ± 33.5	0.542
Prime volume (mL)	1,535 ± 228	1,563 ± 253	0.529
RAP used	222 (86)	204 (90)	0.187
RBC prime	24 (9.3)	23 (10.1)	0.757
Transfused	109 (42)	115 (51)	0.063

GDP: goal-directed perfusion; RAP: retrograde autologous priming; RBC: red blood cell; SD: standard deviation.

Values are mean ± SD or n (%).

Table 3. Outcomes of interest

Variables	Pre-GDP (n = 257)	Post-GDP (n = 226)	p value
Min. DO_2 (L/min/m^2)	238 ± 37.3	278 ± 43.9	<0.001
Min. CPB Hg (g/dL)	7.55 ± 1.25	8.47 ± 1.38	<0.001
Min. CI (L/min/m^2)	2.04 ± 0.15	2.12 ± 0.17	<0.001
Postoperative ΔSCr (%)	135 ± 47.7	125 ± 41.2	<0.001
AKI incidence	111 (43)	65 (29)	0.001
AKI Stage 1	90 (35)	52 (23)	0.004
AKI Stage 2	18 (7.0)	11 (4.9)	0.322
AKI Stage 3	3 (1.2)	2 (0.9)	0.757
Mortality (30 days)	4 (1.6)	1 (0.5)	0.238

DO_2: delivered oxygen; GDP: goal-directed perfusion; CPB: cardiopulmonary bypass; CI: cardiac index; SCr: serum creatinine; AKI: acute kidney injury; SD: standard deviation.
Values are mean ± SD or n (%).

Outcomes of interest

The effectiveness of the QI initiative was assessed by determining (1) the success of DO_2 GDP at increasing the minimum DO_2 during CPB and (2) whether this increase was associated with improved outcomes. Table 3 summarizes these outcomes of interest and differences between the two study groups.

As expected, the minimum DO_2 during CPB increased significantly after implementation of DO_2 GDP ($p < 0.001$). Accordingly, both primary determinants of DO_2, hemoglobin during CPB and pump index, increased significantly ($p < 0.001$, respectively). In the pre-GDP group, 19.5% (50/257) of patients met the target threshold of $DO_2 > 270$ mL/min/m^2 for all measurements during CPB, compared to 50.9% (115/226) of patients in the post-GDP group.

Implementation of DO_2 GDP resulted in a significantly decreased postoperative elevation in SCr as well

as AKI incidence ($p < 0.001$ and $p = 0.001$, respectively). When observing AKI rates at each individual AKIN stage of severity, a decrease in incidence was observed for all three stages. While AKI Stage 1 incidence significantly decreased, in the case of Stage 2 and Stage 3, we found the rarity of these events precluded statistical significance ($p = 0.004$, $p = 0.322$, and $p = 0.757$, respectively). Similarly, while 30-day mortality also decreased, there were too few instances of 30-day mortality to meaningfully statistically analyze.

The probit model results are presented in *Model 1* of Table 4. The coefficient for mean DO_2 was negative and significant (−0.004, $p = 0.031$), which suggests higher levels of DO_2 reduce the risk of AKI. The coefficients for eGFR and anemia were positive and significant (0.005, $p = 0.003$ and 0.299, $p = 0.021$, respectively). The coefficient for utilization of GDP was negative and significant (−0.237, $p = 0.060$), suggesting that the risk of AKI decreased with implementation of GDP. Finally, the coefficient for MAP was not statistically significant. Predicted incidence of AKI was 46% for mean $DO_2 = 200\,mL/min/m^2$; predicted incidence of AKI decreased to 19% for mean $DO_2 = 425\,mL/min/m^2$.

The ordered probit model results are presented in *Model 2* of Table 4. They are qualitatively similar to those for the probit model. We estimated the results using a logistical regression and ordered logistical regression as tests of robustness. The results for mean DO_2 were similar except in the ordered logit model, the negative coefficient for mean DO_2 was of marginal significance ($p = 0.051$).

Table 4. Probit modeling results

Variables	Model 1	Model 2
Mean DO_2 (L/min/m^2)	−0.004**	−0.003**
	(0.002)	(0.002)
eGFR	0.005***	0.002**
	(0.002)	(0.001)
Anemia	0.229**	0.229*
	(0.130)	(0.126)
Utilization of GDP	−0.237*	−0.161
	(0.126)	(0.121)
MAP	−0.004	−0.006
	(0.009)	(0.008)
n	479	479
log_pseudolikelihood	−297.90	−389.55
Wald test (χ^2)	30.76****	24.55****

DO_2: delivered oxygen; eGFR: estimated glomerular filtration rate; GDP: goal-directed perfusion; MAP: mean arterial pressure; AKI: acute kidney injury.
Robust standard errors in parentheses. The dependent variable in *Model 1* is AKI (0 = no AKI, 1 = AKI). The dependent variable in *Model 2* is AKI stage (0 = no AKI, 1 = AKI Stage 1, 2 = AKI Stage 2 or 3). *Model 1* is estimated with a probit model, while *Model 2* is estimated with an ordered probit model.
*$p < 0.1$, **$p < 0.05$, ***$p < 0.01$ ****$p < 0.001$.

Discussion

The role of DO_2 in CPB-induced AKI

The pathogenesis of AKI occurring status post CPB is well studied despite being incompletely understood. Factors inherent to CPB which are known to contribute to injury include both decreased renal blood flow and MAP, which in turn place nephrons at risk of ischemic injury and decrease the transluminal pressure gradient allowing for glomerular filtration.[12] The process by which AKI occurs is described in five clinical phases: prerenal, initiation, extension, maintenance, and repair.[13] In the prerenal phase, cellular and vascular adaptive processes prevent injury and preserve function despite insults, which eventually exceed the capacity of these adaptive processes and lead to the initiation phase. This second phase is characterized by ischemic ATP depletion and oxidative injury to both the tubular epithelium and renal vascular endothelium. Injury to the latter exacerbates inflammatory cascades and medullary congestion extending injury to the corticomedullary junction and eventually furthering injury to the proximal tubule. Acute tubular necrosis results and is characterized by the formation of granular casts of sloughed, necrotic, tubular epithelial cells; the resulting obstruction of tubules and denudation of the tubular basement membrane inhibits glomerular filtration and causes a "back flow" of filtrate across the tubular basement membrane.[12,14] Resolution occurs with proliferation and redifferentiation of tubular epithelium (maintenance phase) followed by resumed polarity and function (repair phase).[13]

Use of CPB involves a state of decreased cardiac output, hemoglobin, MAP, and loss of pulsatility (excepting the use of intra-aortic balloon pump (IABP) or pulsatile pump modes); all of which may contribute to the pathogenesis of AKI.[15] It has been established that extreme hemodilution may contribute to AKI despite theoretical renal protective benefits such as reduced blood viscosity and improved regional blood flow in the setting of hypoperfusion and hypothermia.[16] Furthermore, the risk of AKI due to hemodilution is decreased with increased pump flow, suggesting that the contribution of both as described in the DO_2 equation underlies their role in causing AKI and that manipulation of perfusion practices via GDP could decrease the incidence of AKI.[16,17] We set out to implement DO_2 GDP at our institution with this in mind.

It is notable that the relationship between DO_2 and AKI incidence is complicated and non-linear. For example, time is an important component of AKI risk. Patients who spend a very short time with subthreshold

DO_2 are expected to have a lower AKI incidence than patients who spend extended periods of time with subthreshold DO_2 perhaps even when the minimum DO_2 was greater. Whereas minimum DO_2 does not account for this time component, mean DO_2 (as used in the probit model) does at least in an inexact way by "weighing" repeated subthreshold measurements.

Assessment of QI initiative

Differences in preoperative kidney function were noted between the two groups, but these differences were not found to be independent predictors of AKI. These results suggest that the post-GDP group had worse preoperative kidney function but that this did not influence the relative likelihood of AKI status post CPB for either group.

The increase in minimum DO_2 in the post-GDP group was notable not only for the significance of the increase by 40 mL/min/m^2 ($p < 0.001$) but also because it resulted in the mean for the post-GDP group exceeding the goal of 270 mL/min/m^2 as AKI incidence was expected to decrease at this point. This level represented a critical value below which the risk of AKI is inversely correlated with DO_2. These changes reflected practices undertaken by our perfusionists to maintain a higher flow rate and minimize hemodilution.

The corresponding decrease in postoperative change in SCr and AKI incidence signified the complete success of the QI initiative. Had the incidence of AKI observed retrospectively in the pre-GDP group been observed in the post-GDP group, 97 cases of AKI would have been expected. From this, we conclude that the QI initiative may be credited with preventing as many as 32 cases of AKI at our institution between February 2017 and June 2018. The decrease in AKI incidence from 43% to 29% following implementation of DO_2 GDP yields a number needed to treat of 6.9, which is to say that compared to perfusion practices prior to the implementation of DO_2 GDP, current perfusion practices are expected to prevent one case of AKI for every 6.9 patients in our population.

It is worth noting that our population is at particularly high risk of AKI given high incidences of comorbidities such as anemia and DM. This increased risk, along with the comparatively conservative criteria that AKIN uses to define AKI (in contrast to other criteria, for example, The Society of Thoracic Surgeons National Database), largely explains our institution's rate of AKI in comparison with overall incidences reported in the literature. Moreover, the higher incidence of anemia in part explains a higher incidence of RBC transfusions. In facing the risks associated with transfusions, clinicians and the entire surgical team were forced to weigh the consequences of failing to maintain adequate DO_2 with these risks. As a result, the fact that only 50.9% (115/226) of patients in the post-GDP group met the DO_2 threshold for all measurements is in part a reflection of the need to balance these risks in each clinical scenario.

Limitations

This study did not take the form of a randomized control trial, and therefore the conclusions that we may draw from our results are limited. The institution has purchased the Epic© (Epic Systems Corporation, Verona, Wisconsin, USA) charting system however, at the time of this writing the perfusionists used a handwritten record, which will include intermittent entries, missed entries, and bias associated with nadir values. Intermittent entries were also a consequence of intermittent sampling of blood for blood gas analysis, which occurred at 30-minute intervals. While clinicians were able to monitor, interpret, and respond to real-time data indicating the adequacy of perfusion via CDI 500, such Hg measurements were subject to a degree of inaccuracy relative to the approved point of care (POC) blood gas analysis. However, limiting data collection to 30-minute intervals is disadvantageous in that it restricts postoperative analysis of DO_2 to discrete intervals.

Urinary output measurements as obtained perioperatively were not suitable for determining AKI using the AKIN criteria as they are inherently and unacceptably imprecise and discrete with significant time intervals between measurements. As a result, it can be assumed that some cases of AKI that met only urinary output criteria and not SCr criteria were not captured and thus AKI incidence was underestimated for both groups.

SCr measurements were recorded for the duration of the hospitalization including measurements a couple weeks after surgery. In reviewing patterns of postoperative change in SCr, peaks were consistently seen in the first 72 hours and, occasionally, later in the hospitalization. To capture only cases of AKI related to CPB effects and not those due to other, more remote sequelae, we chose to use only the first 72 hours of SCr measurements in determining whether AKI had occurred. Again, it is possible that this underestimated AKI incidence for both groups.

Future work

No attempt was made in this study to elucidate the contributions of increased pump flow and decreased hemodilution independently. As a result, we cannot state to what extent the observed decrease in postoperative change in SCr and AKI incidence was due to increased pump flow versus decreased hemodilution; however, the literature supports the theory that both played some role.

This inability to independently assess the roles of hemodilution and low pump flow in causing AKI during CPB represents an opportunity for additional

study. To that end, more work is needed to determine the relative contributions of each of these variables in causing AKI, as well as determining whether one has a greater impact than the other under certain conditions (e.g. patients with pre-existing comorbidities such as DM with varying levels of severity, patients receiving blood products, patients with very high or very low BMI, and surgeries with extended pump times). Moreover, other variables related to CPB that are theorized to impact AKI risk, such as MAP, warrant additional scrutiny.

Conclusion

AKI status post CABG is a serious adverse outcome of CPB and its incidence is high enough to warrant significant scrutiny in CPB decision making. Intraoperative DO_2 is known to play an important role in the pathogenesis of postoperative AKI, and by applying this understanding to the implementation of a QI initiative to prevent inadequate intraoperative DO_2, AKI incidence was dramatically reduced at our institution.

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Declaration of Conflicting Interests

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References

1. McIlroy DR, Argenziano M, Farkas D, et al. Incorporating oliguria into the diagnostic criteria for acute kidney injury after on-pump cardiac surgery: impact on incidence and outcomes. *J Cardiothorac Vasc Anesth* 2013; 27: 1145–1152.
2. Lagny MG, Jouret F, Koch JN, et al. Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification. *BMC Nephrol* 2015; 16: 76–79.
3. Li SY, Chen JY, Yang WC, et al. Acute kidney injury network classification predicts in-hospital and long-term mortality in patients undergoing elective coronary artery bypass grafting surgery. *Eur J Cardiothorac Surg* 2011; 39: 323–328.
4. Lopez-Delgado JC, Esteve F, Torrado H, et al. Influence of acute kidney injury on short- and long-term outcomes in patients undergoing cardiac surgery: risk factors and prognostic value of a modified RIFLE classification. *Crit Care* 2013; 17: R293.
5. Alshaikh HN, Katz NM, Gani F, et al. Financial impact of acute kidney injury after cardiac operations in the United States. *Ann Thorac Surg* 2018; 105: 469–475.
6. Ranucci M, Romitti F, Isgro G, et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. *Ann Thorac Surg* 2005; 80: 2213–2220.
7. Long DM, Jenkins E, Griffith K. Perfusionist techniques of reducing acute kidney injury following cardiopulmonary bypass: an evidence-based review. *Perfusion* 2015; 30: 25–32.
8. Ranucci M, Johnson I, Willcox T, et al. Goal-directed perfusion to reduce acute kidney injury: a randomized trial. *J Thorac Cardiovasc Surg* 2018; 156: 1918–1927.
9. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–381.
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.
11. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11: R31.
12. Moran SM, Myers BD. Pathophysiology of protracted acute renal failure in man. *J Clin Invest* 1985; 76: 1440–1448.
13. Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney Int* 2002; 62: 1539–1549.
14. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephro* 2006; 1: 19–32.
15. Ranucci M. Perioperative renal failure: hypoperfusion during cardiopulmonary bypass. *Semin Cardiothorac Vasc Anesth* 2007; 11: 265–268.
16. Swaminathan M, Phillips-Bute BG, Conlon PJ, et al. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. *Ann Thorac Surg* 2003; 76: 784–791; discussion 792.
17. de Somer F, Mulholland JW, Bryan MR, et al. O2 delivery and CO2 production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management. *Crit Care* 2011; 15: R192.

Discussion: Using a quality improvement initiative to reduce acute kidney injury during on-pump coronary artery bypass grafting

Presenter, *Mitchell Katona*

Mr Alfred Stammers (Sweet Valley, Pennsylvania): Thanks to your and Joshua Walker's work on showing the value of using a cQI program and prospectively collecting data to address some questions and gaps in the literature. I have a question concerning the impact of hemoglobin. The cardiopulmonary bypass (CPB) red blood cell rate seemed very high with 9-10% of the patients receiving red blood cells in the pump prime. I assume that these were all patients coming for cardiac surgery not just isolated coronary artery bypass grafting (CABG) patients.

Mr Mitchell Katona (San Antonio, Texas): No. This was strictly a study of patients receiving isolated CABG.

Mr Stammers: That is an extremely high rate for patients receiving isolated CABG who usually have a median starting hematocrit around 35%. What is your criterion for transfusing patients? What was the percentage of transfusions that occurred in the pre-GDP (goal-directed perfusion) versus post-GDP period?

Mr Katona: The criterion available to us to make that decision whether to transfuse for the purposes of GDP a delivered oxygen less than 270 mL/min in the absence of any contraindications to transfusion would have been that alternative strategy to raise delivered oxygen above our goal of 270 mL/min.

Mr Stammers: You were able to raise delivered oxygen with blood flow and not blood transfusion?

Mr Katona: That is correct.

Mr Stammers: So transfusion was the secondary response to go ahead and reach 270 mL/min that way?

Mr Katona: Yes.

Mr Stammers: Your results show that 9-10% of your study patients were receiving red blood cells in the CPB prime, which seems extremely high. Is this intraoperatively?

Mr Katona: Yes.

Mr Stammers: Those intraoperative values are two-and-one-half times the national average reported by the Society of Thoracic Surgeons. I just wonder with this particular patient population that were so highly transfused, if you would reduce transfusions to a more normal rate would you see a change in outcomes overall?

Mr Katona: That is a good point and one that we should look at closer—namely, the increased rate of red blood cells added in the pump prime.

Mr Joshua Walker (San Antonio, Texas): I would like to address Mr Stammer's comment. We noted that our patients were extraordinarily anemic. This particular patient population in San Antonio tends to be of short stature and very rotund, to use the correct term, so we try to optimize our prime. Our CPB priming volume is high, and we do employ retrograde autologous priming (RAP). The volume was recorded primarily because of the variability I discovered when reviewing our charts. I noticed that each perfusionist recorded it a little differently, and it became very difficult for me to clearly understand what was there. So we decided to use RAP as a binary—that is, was it done or not done, and we did it on just about all study patients. Whether it was 300 or 800 mL is a whole other discussion as to whether there was too much RAP. We do have a patient population with a baseline hematocrit of 30-33% coming into the operating room. By the time anesthesia personnel administer crystalloid solution and before the patients are placed on CPB they typically have a starting hematocrit of 26-27%, which explains why our percentage of patients who received red blood cells in their CPB prime is so much higher. We acknowledge that factor.

Mr Harry McCarthy (Richmond, Virginia): How were you able to standardize measurements from your cohort that was prior to the study to post-study? Were they recorded at the same interval or was there a way to standardize the length of time patients may have been at this reduced level of delivered oxygen?

Mr Katona: Are you asking how did we standardize the measurement for delivered oxygen?

Mr McCarthy: Yes. The blood flow, hemoglobin, and delivered oxygen pre-initiation of the study, prior to February 2017, and post.

Mr Katona: We used serial blood gases every 30 minutes to determine real-time delivered oxygen, and we were looking at nadir delivered oxygen. The time spent was not something we necessarily were considering, but at any point falling below 270 mL/min would have been considered an undesirable outcome.

Mr McCarthy: Did you change your measurement strategy at all from the group that was being pre-studied to the post-study?

Mr Katona: No, we did not change that strategy.

This discussion is taken from the dialogue that followed the presentation of the previous paper at the 40th Annual Seminar of the American Academy of Cardiovascular Perfusion. Although the paper has been through *Perfusion*'s stringent peer-review process, the discussion is a transcript of the dialogue, edited for clarity, and the views expressed in the discussion are those of the commentators and do not necessarily represent and should not be attributed to the journal *Perfusion*, the Editors, authors or the Publisher, SAGE.

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Acute kidney injury, stroke and death after cardiopulmonary bypass surgery: the role of perfusion flow and pressure

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Abstract

Introduction: Acute kidney injury after cardiopulmonary bypass surgery is associated with morbidity and mortality. This study aims to evaluate the role of low perfusion flow and pressure in the development of cardiopulmonary bypass–associated acute kidney injury, stroke and death, using multicentre registry data.

Methods: We identified patients from the Australian and New Zealand Collaborative Perfusion Registry who underwent coronary artery bypass grafting and/or valvular surgery between 2008 and 2018. Primary predictor variables were the length of time the perfusion flow was <1.6 L/min/m^2 and the length of time perfusion pressure was $<$ 50mmHg. The primary outcome was new postoperative acute kidney injury defined by the risk-injury-failure-loss-end stage criteria. Secondary outcomes were stroke and in-hospital death. The influence of perfusion flow and pressure during cardiopulmonary bypass on the primary and secondary outcomes was estimated using separate multivariate models.

Results: A total of 16,356 patients were included. The mean age was 66 years and 75% were male. Acute kidney injury was observed in 1,844 patients (11%), stroke in 204 (1.3%) and in-hospital death in 286 (1.8%). Neither the duration of the time spent for perfusion flow (<1.6 L/minute/m^2) nor the duration of the time spent for perfusion pressure ($<$50 mmHg) was associated with postoperative acute kidney injury, stroke or death in adjusted models.

Conclusions: Neither low perfusion pressure nor low perfusion flow during cardiopulmonary bypass were predictive of postoperative acute kidney injury, stroke or death.

Keywords

acute kidney injury; perfusion flow; perfusion pressure; cardiopulmonary bypass; stroke

Introduction

Cardiac surgery employing the use of cardiopulmonary bypass (CPB) is common in Australia. The incidence of acute kidney injury (AKI) associated with cardiac surgery is variably reported, but has been documented as high as 30%.[1,2] It is well established in the literature that AKI following cardiac surgery is associated with increased morbidity and mortality.[1–3] While AKI requiring dialysis is infrequent, a small rise in creatinine postoperatively is common. Even with complete or partial recovery, AKI is associated with longer ICU stay, longer hospital stay, increased risk of myocardial infarction, and increased mortality at 30 days.[1,4]

There are many factors that may contribute to AKI following cardiac surgery including patient comorbidities, intra-aortic balloon pump (IABP) use, CPB duration,[2] intraoperative blood transfusion,[5] haemodilution,[6] hyperthermic perfusion[7] and oxygen delivery.[8] Perfusion

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flow and pressure during CPB represent some of the less well understood intraoperative variables in terms of their impact on renal perfusion and, as a consequence, there is 'limited evidence to make strong recommendations regarding how to conduct CPB in regards to perfusion flow and pressure'.[1] Previous studies evaluating perfusion flow and pressure are largely based on cerebral perfusion and therefore the true impact of low perfusion flow and pressure on renal function is not well understood.

Understanding CPB-associated AKI is becoming increasingly important due to the ageing population and increasing rates of chronic disease, meaning that more patients are predisposed to AKI due to pre-existing renal dysfunction.[1] This research has important clinical applications in helping to evaluate the risk factors for developing CPB-associated AKI, with the overall aim of improving patient outcomes.

Using multicentre registry data, we aimed to evaluate the role of perfusion pressure and flow in the development of CPB-associated AKI.

Methods

Setting and participants

This was a multicentre binational retrospective cohort study. Data were obtained from The Australian and New Zealand Collaborative Perfusion Registry (ANZCPR) which is a project conducted by the ANZCPR Steering Committee in conjunction with Perfusion Downunder Collaboration (PDUC). ANZCPR maintains a non-identifiable prospective data set on all cardiac surgical procedures performed on patients over the age of 18 years in multiple sites throughout Australia and New Zealand since 2007.[9]

Patients from the registry who underwent coronary artery bypass grafting (CABG) and/or valvular repair or replacement using CPB over a 10-year period from January 2008 to February 2018 were included in the study. Patients from the registry were excluded from this study if they did not undergo CABG and/or valve surgery or if they were missing data or any variables that were included in the multivariate model because of their relationship between pressure, flow and AKI.

The study was approved by the Tasmanian Human Ethics Committee Network (Approval No. H0017147, Date of Approval: 23 May 2018).

Variables, data source and definitions

ANZCPR uses Microsoft Access for data entry interface, storage and transfer. The database is able to accept the direct transfer of electronic data from the heart lung machine.[10,11] Clinical data definitions were based on the Australian and New Zealand Society of Cardiothoracic Surgeons registry https://anzscts.org/database/about/#DDM (accessed 29 October 2019). Complete ANZCPR variable definitions are available at https://www.anzcpr.org/documents (accessed 30 October 2019).

Primary predictors: perfusion flow and pressure. Flow and pressure during CPB were sampled electronically every 20-60 seconds by the heart lung machine. Low perfusion flow was defined as an indexed flow (i.e. cardiac index) <1.6 L/minute/m^2. Low perfusion pressure was defined as a blood pressure <50 mmHg.[11] Data presented are total duration of time below these cut-offs, or mean (SD) flow or pressure. During the period of weaning from CPB, low flow may not accurately represent systemic blood flow due to the contribution of native cardiac output. For this reason, the ANZCPR exclude flow data during CPB weaning as defined by documentation of partial bypass in the CPB record.

Primary outcome: AKI. The serum creatinine (sCr) baseline was defined as the preoperative value collected closest to the day of surgery. Postoperative sCr was defined as the maximal postoperative value. The early risk-injury-failure-loss-end stage (RIFLE) classification of AKI was used. This defines three grades of increasing severity of AKI (R, I and F), according to an increase in sCr of $>50\%$, $>100\%$ and $>200\%$, respectively.[12] Individuals' postoperative sCr to preoperative sCr ratio was analysed as a continuous variable. Urine output data are not available in the registry and are therefore not included in the RIFLE definition of AKI. AKI of any RIFLE classification (based on sCr alone) was used as the primary endpoint. The RIFLE criteria was chosen as it has been widely validated for its use in determining the incidence of AKI and prognostic stratification in the acute hospital setting[13] and it continues to be widely utilised in cardiac surgery research.[12,14]

Secondary outcomes: stroke and death. Secondary outcomes included stroke and death. Stroke was defined as a new central neurologic deficit persisting for greater than 72 hours that occurred as an inpatient postoperatively. Death included all causes of in-hospital death.

Statistical analysis

The distribution of characteristics for those with and without AKI were compared using t-tests for normally distributed continuous variables, rank-sum tests for non-normal data and chi-square tests for categorical data. Linear regression models were used to estimate the influence of flow and pressure separately on the primary outcome of AKI. Log transformation of both predictor and outcome was required to correct for skew and meet

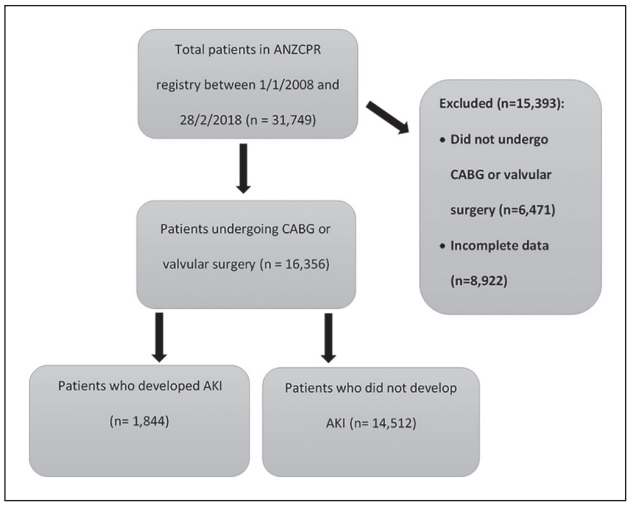

Figure 1. Patients flowchart.

the assumption of normal residuals. A transformation of $\ln(1+x)$ was used for the predictors to allow for zero values of time at low flow or pressure. A robust estimate of the variance allowing for correlation within the nine hospitals was used, and inverse propensity weights to address potential bias from missing data observations was applied. Confounding variables were identified using univariate tests of association between outcomes and the predictors of interest, from a list of demographic, preoperative and intraoperative factors identified a priori. A multivariable model adjusting for demographic and comorbidities was built for each of the predictors of interest to provide an estimate of the effect of low flow or low pressure independent of these factors, and then a model additionally adjusted for a set of intraoperative variables to isolate the effect of the predictor of interest independent of other operative factors. Interactions between flow and pressure and nonlinear terms were also tested. Model residuals were assessed, and values of R^2 used as a measure of outcome variance were explained. In sensitivity analyses, models were run with alternative measures of low flow ($<$1.8 and 2.0 L/minute/m^2) and pressure ($<$30 and $<$40 mmHg). Stata 15.1 (Texas, USA) was used for statistical analysis.

Results

A total of 31,749 patients over the age of 18 were included from the registry between January 2008 and February 2018. Of these, 16,356 meet our inclusion criteria (Figure 1). There were 6,471 patients excluded from our study because they did not undergo CABG and/or valve surgery and 8,922 were excluded because they were missing data related to pressure, flow and AKI (Figure 1). The majority of missing data were attributed to the fact that those variables (peripheral vascular disease, cardiogenic shock, New York Heart Association (NYHA) classification) were not included in the initial registry data set (n = 3,583) or due to a data transfer error at one site affecting the variables such as severe neurological dysfunction, critical pre-op state and NYHA classification (n = 2,695). Outcomes data were not collected at one site for 831 patients.

The median age of patients was 68 years (interquartile range (IQR) 60-75) and 12,220 (74.7%) patients were male. Age and gender distribution in our study population were reflective of the overall registry population and consistent with other Australian studies.[1] Preoperative, procedural and intraoperative characteristics of the study population are outlined in Table 1.

Primary outcomes. Of the 16,356 patients, 1,844 (11.3%) developed AKI, with 1,272 (7.8%) stage 'Risk', 434 (2.7%) stage 'Injury' and 138 (0.8%) stage 'Failure' (Table 2). There were clinically significant preoperative differences between patients developing AKI compared to those who did not (Table 1). Patients with AKI were older, more likely to have pre-existing comorbidities, had a lower left ventricular ejection fraction (LVEF) and were more likely to be in a critical preoperative state, compared to patients with no AKI (Table 1).

Intraoperatively, patients with AKI had a longer mean cumulative time with a flow $<$1.6 L/minute/m^2 and a longer mean time with a pressure $<$50 mmHg. There was no clinically significant difference of overall mean flow or pressure between the groups. In a univariable linear regression analysis, both cumulative time spent for a perfusion flow $<$1.6 L/minute/m^2 and time spent for a perfusion pressure $<$50 mmHg were associated with postoperative AKI; however, the magnitude of the effect is very small. In the case of low perfusion flow, the coefficient is 0.018 (95% confidence interval (CI): 0.009, 0.027) as seen in Table 3. Both the outcome and predictor variables modelled here were log-transformed, so the units are not directly interpretable, and the model relationship is nonlinear in the original units. An approximate beta coefficient in the original units for ranges of the predictor can be calculated from the model to aid interpretation: in the range of 0-1 minute, the coefficient is 0.03, which means a 1-minute increase in time spent for low flow is associated with a 0.03 increase in the ratio of sCr or an additional 3% increase in postoperative sCr. In the range of 1-3 minutes, the approximate coefficient is 0.01, and for 3-10 minutes, it is 0.003 or less than 1% increase. This is further demonstrated in Figure 2, which shows that while time spent for a low perfusion flow may result in small postoperative creatinine rise, the difference is not enough to reach diagnostic criteria of AKI, meaning that this slight sCr rise is not of clinical significance against current definitions of AKI. Since there was no effect found in multivariate analysis for the primary endpoint of any AKI, classes of

Table 1. Demographic and clinical characteristics of study population.

Characteristics	No AKI n = 14,454	AKI n = 1,829	p value
Preoperative			
Age (years), mean (SD)	66.1 (12.0)	69.2 (11.8)	<0.001
Male (%)	75.1	71.5	0.001
BMI (kg/m^2), mean (SD)	28.7 (5.4)	30.0 (6.2)	<0.001
Diabetes (%)	30.1	38.1	<0.001
Hypertension (%)	70.5	76.3	<0.001
Current or recent smoker (%)	12.9	11.3	0.055
Peripheral vascular disease (%)	7.4	11.2	<0.001
NYHA class II-IV (%)	63.4	72.0	<0.001
Severe neurological dysfunction (%)	1.8	3.5	<0.001
COPD (%)	12.9	19.5	<0.001
Previous cardiac surgery (%)	5.8	8.1	<0.001
Infective endocarditis (%)	1.5	3.7	<0.001
LVEF <45% (%)	15.7	23.0	<0.001
Congestive cardiac failure (%)[a]	13.3	20.1	<0.001
Pre-op Hb (g/L), mean (SD)	132.7 (17.9)	123.5 (19.5)	<0.001
Pre-op sCr, mean (SD)	101.8 (86.7)	102.5 (55.5)	0.621
Critical pre-op state (%)[b]	3.3	8.5	<0.001
Urgency operation (%)[c]	25.9	30.9	<0.001
Cardiogenic shock (%)	0.8	2.9	<0.001
Procedure			<0.001
CABG only (%)	59.4	48.9	
CABG + valvular surgery (%)	13.5	21.0	
Valvular surgery only (%)	27.1	30.0	
Intraoperative			
CPB duration (minutes), median (IQR)	85 (66-108)	91 (71-120)	<0.001
Time flow (<1.6 L/minute/m^2)			
Mean (minutes) (SD)	4.9 (8.5)	5.7 (9.9)	
Median (minutes) (IQR)	3.0 (1.66-5)	3.0 (1.66-5.99)	<0.001
Time pressure (<50 mmHg)			
Mean (minutes) (SD)	12.5 (13.4)	15.0 (18.6)	
Median (minutes) (IQR)	8.7 (4-16)	9.5 (4.3-18.3)	<0.001
Mean flow (L/minute/m^2) (SD)	4.3 (0.7)	4.4 (0.7)	0.053
Mean pressure (mmHg) (SD)	62.3 (7.3)	61.8 (7.5)	0.003
IAPB (%)	2.5	10.3	<0.001
Hb (<70 g/L) (%)	12.5	23.6	<0.001

AKI: acute kidney injury; SD: standard deviation; BMI: body mass index; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; LVEF <45%: left ventricular ejection fraction <45%; Pre-op Hb: preoperative haemoglobin; Pre-op sCr: preoperative serum creatinine; CABG: coronary artery bypass grafting; CPB duration: cardiopulmonary bypass duration; IQR: interquartile range; IABP: intra-aortic balloon pump; Hb: haemoglobin.

[a]Whether a physician has ever diagnosed congestive heart failure by one of the following: 1. paroxysmal nocturnal dyspnoea; 2. dyspnoea on exertion due to heart failure; 3. chest X-ray showing pulmonary congestion, or 4. patient has received treatment for this– Angiotensin converting enzyme (ACE) inhibition, diuretics, carvedilol or digoxin.

[b]Any of the following immediately prior to surgery: ventricular tachycardia/ventricular fibrillation or aborted sudden death, cardiac massage, ventilation before anaesthetic room, inotropes or IABP.

[c]Surgery characterised as elective (could be deferred without risk of compromised cardiac outcome) or urgent (within 72 hours angiography or required to minimised chance of further deterioration in a comprised patient, unscheduled surgery on the same day as admission due to refractory angina or haemodynamic compromise or patient underwent CPR prior to surgery).

AKI with lower incidence (injury, failure) were not evaluated.

In models adjusted for demographic and comorbidities (Table 3), the effects for time spent for low flow and time spent for low pressure were attenuated, and in fully adjusted models including intraoperative variables, these effects completely disappeared. There was no significant interaction observed between low flow and low pressure, regardless of the measures used.

Other risk factors for AKI and sensitivity analysis. Age, diabetes, use of an IAPB, Hb <100 g/L and CPB duration

Table 2. Incidence of AKI, stoke and death in the analysis sample.

Outcome	No AKI (n = 14,512)	AKI (n = 1,844)
Acute kidney injury		1,844 (11%)
Risk (>50% increase in sCr)		1,272 (7.8%)
Injury (>100% increase in sCr)		434 (2.7%)
Failure (>200% increase in sCr)		138 (0.8%)
Stroke	146 (1%)	58 (3.1%)
Death	146 (1%)	140 (7.6%)

AKI: acute kidney injury.

Table 3. Univariate and multivariate linear regression analysis with AKI as the outcome variable.

	Univariate linear regression		Semi-adjusted multivariate linear regression[a]		Multivariate linear regression[b]	
	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
Time (minutes) spent for perfusion flow <1.6 L/minute/m^2 (log)	0.018 (0.009, 0.027)	0.002	0.011 (0.004, 0.018)	0.006	0.000 (−0.007, 0.007)	0.944
Time (minutes) spent for perfusion pressure <50 mmHg (log)	0.008 (−0.003, 0.018)	0.142	0.007 (−0.004, 0.017)	0.183	0.000 (−0.011, 0.012)	0.925

CI: confidence interval.

[a]Adjusted for demographic and comorbidities variables (sex, age, severe neurological disease, previous cardiac surgery, infective endocarditis, critical preoperative state, categorical estimation of ejection fraction (EF)%, urgency of operation, patient on dialysis preoperatively, diabetes, congestive heart failure, NHYA classification, peripheral vascular disease, most recent preoperative Hb (g/L) and cardiogenic shock at time of procedure).

[b]Adjusted for demographic, comorbidities and intraoperative variables (procedure, procedure type, total time on bypass, Hb during CPB <70 g/L and time of earliest IABP insertion).

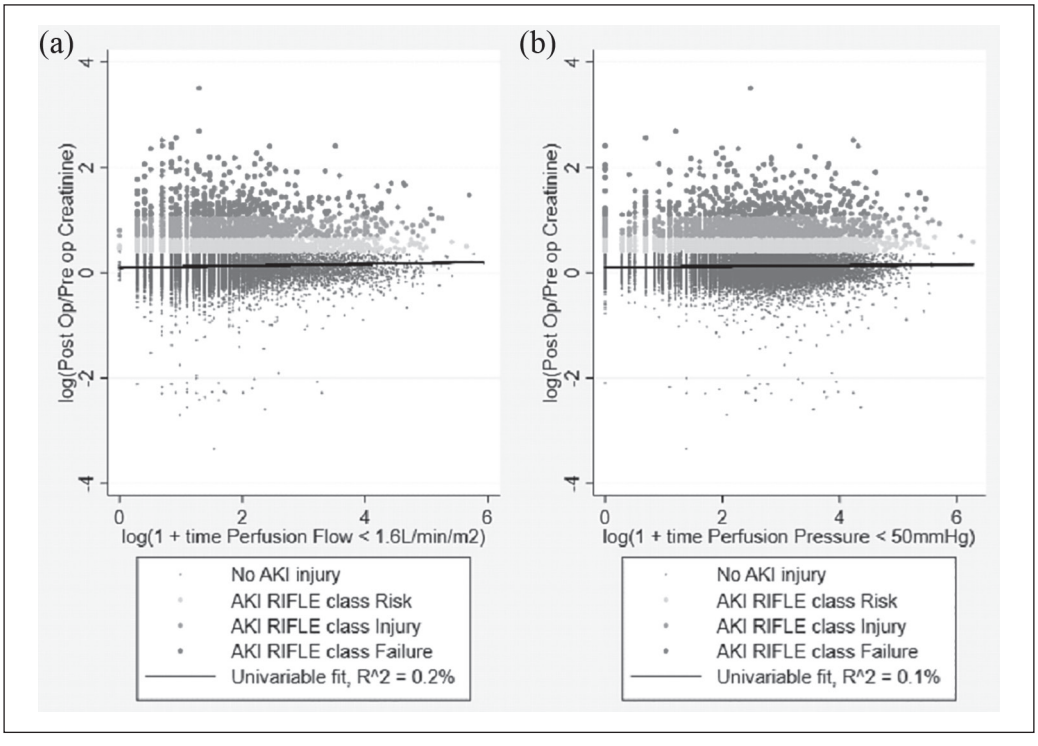

Figure 2. Scatter plot of the primary predictors of interest against the pre-to-postoperative sCr ratio used in the RIFLE criteria, and the univariable linear regression fit: (a) accumulated time (minutes) spent for perfusion flow <1.6 L/minute/m^2 (log) versus sCr ratio (log) and (b) accumulated time (minutes) spent for perfusion pressure <30 mmHg (log) versus sCr ratio (log).
The plotted model fit (black line) shows that no clinically relevant duration of time spent for low flow or pressure is enough on its own to cause AKI according to the RIFLE diagnostic criteria.

Table 4. Univariate and multivariate logistic regression analysis with stroke and death as the outcome variables.

	Stroke				Death			
	Univariate logistic regression		Multivariate logistic regression[a]		Univariate logistic regression		Multivariate logistic regression[b]	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Time (minutes) spent for perfusion flow <1.6 L/minute/m^2 (log)	1.49 (1.10, 2.03)	0.01	1.26 (0.97,1.65)	0.083	1.74 (1.36, 2.23)	<0.001	1.20 (0.98, 1.46)	0.071
Time (minutes) spent for perfusion pressure <50 mmHg (log)	1.22 (0.93, 1.60)	0.158	1.08 (0.86, 1.37)	0.487	1.50 (1.03, 2.19)	0.035	1.01 (0.78, 1.32)	0.916

OR: odds ratio; CI: confidence interval.

[a]Adjusted for demographic, comorbidities and intraoperative variables (sex, age, severe neurological disease, previous cardiac surgery, infective endocarditis, critical preoperative state, history of stroke, cerebrovascular disease, congestive heart failure, NHYA classification, most recent preoperative Hb (g/L) and cardiogenic shock at time of procedure, procedure type, total time on bypass, Hb during CPB <70 g/L and time of earliest IABP insertion).

[b]Adjusted for demographic, comorbidities and intraoperative variables (sex, age, severe neurological disease, previous cardiac surgery, infective endocarditis, critical preoperative state, categorical estimation of EF%, urgency of operation, patient on dialysis preoperatively, congestive heart failure, NHYA classification and cardiogenic shock at time of procedure, procedure type, total time on bypass, pH during CPB <7.35 or >7.45 mmHg, Hb during CPB <70 g/L and time of earliest IABP insertion).

explained the most variance in postoperative sCr in a multivariate model for AKI predictors (Table 1 of Supplemental Appendix 1)

A sensitivity analysis was conducted using different definitions of low flow (<1.8 L/minute/m^2; <2 L/minute/m^2) and pressure (<30 mmHg; <40 mmHg). The study findings remained essentially unchanged in the sensitivity multivariate model.

Secondary outcomes. Two hundred and four patients developed stroke (1.3%) and 286 (1.8%) died during their hospital admission (Table 2). Table 4 demonstrates that in a multivariable linear regression analysis, time spent for perfusion pressure (<50 mmHg) or time spent for perfusion flow (<1.6 L/minute/m^2) was not associated with stroke or death.

Discussion

Summary of results

This binational retrospective cohort study suggests that neither the time spent for perfusion flow (<1.6 L/minute/m^2) nor the time spent for perfusion pressure (<50 mmHg) during CPB was predictive of postoperative AKI, stroke or death.

Of the 16, 356 patients in our study, 1,844 (11.3%) developed AKI. Patients who developed AKI were older, more likely to have pre-existing comorbidities, had a lower LVEF and were more likely to be in a critical preoperative state, compared to patients with no AKI. In a univariable linear regression analysis, both cumulative time spent for a perfusion flow <1.6 L/minute/m^2 and time spent for a perfusion pressure <50 mmHg were associated with postoperative AKI; however, the magnitude of the effect is very small and in fully adjusted models including intraoperative variables these effects completely disappeared.

Age, diabetes, use of an IAPB, Hb <100 g/L and CPB duration explained the most variance in postoperative sCr in a multivariate model for AKI predictors.

Correlation to other studies and significance of our results

The factors that contribute to AKI following CPB are complex and multifactorial.[15] There are well established risk prediction scores for AKI that include both patient and operative characteristics,[16] but most of these variables are fixed or not amenable for intervention. Our data confirm the importance of these predictors (Table 1 of Supplemental Appendix 1). Age, diabetes, preoperative Hb <100 g/L, CPB duration and the use of an IABP were among the independent predictors that were statistically significant (Table 1 of Supplemental Appendix 1). These findings are consistent with previous literature.[2] Intraoperative CPB perfusion flow or pressure are not included in these predictive scores but are amenable to intervention and therefore a better understanding of their influence on postoperative AKI is warranted. Our results found that low perfusion flow and pressure were not independent predictors of AKI. Furthermore, we found that any impact of low flow and pressure on postoperative creatinine, albeit small, is diminished in a fully adjusted multivariate model (Table 3). Our multivariate

analysis (adjusted for demographics and comorbidities) found that clinically relevant preoperative factors including age, diabetes, LVEF <45% and a critical preoperative state have the greatest ability to predict postoperative creatinine.

Evidence describing the influence of perfusion pressure and flow on end-organ perfusion during CPB is limited.[17] Autoregulation of renal blood flow and glomerular filtration rate is blunted during CPB by the combined effects of haemodilution and nonpulsatile blood flow.[18] Therefore, control of blood pressure or flow to enhance renal oxygen delivery may be critical in the prevention of AKI. It is not clear which of these is most important and whether a universal absolute lower threshold (as we have used in this study) or an individualised relative change is the major factor. Bojan et al.[19] reported that maintaining the perfusion pressure above 60% of the age-standardised mean arterial pressure may be an effective renal protective strategy. Ono et al.[20] suggest that excursion of mean arterial blood pressure below the limit of cerebral autoregulation (rather than absolute mean arterial pressure) is independently associated with AKI. However, Slogoff et al.[3] demonstrated similar findings to that of our analysis, in that neither low pressure nor low flow was predictive of postoperative creatinine in 504 adults undergoing cardiac surgery. By comparison, Fischer et al.'s study suggested that those with CPB-associated AKI had a lower mean CPB flow and a longer time with a perfusion pressure <60 mmHg. However, their analysis did not adjust for some key confounding variables.[21]

Our results are consistent with recently published ANZCPR findings by Newland et al.[22] that in a multivariate analysis, the effect of perfusion pressure on AKI was attenuated. It should be noted that Newland et al.'s[22] study used different models as the primary predictor of interest was oxygen delivery. Oxygen delivery was not included as a covariate in our multivariate model since the effect size for pressure and flow in the univariate analyses was very small. With the addition of other fundamental demographic and intraoperative covariates, the effect was removed; therefore, given the influence of oxygen delivery on AKI inclusion of further covariates in the model was not warranted. However, as this is currently highly topical, the influence of the minimum oxygen delivery index (DO_{2i}) on the development of AKI could be revaluated in a subsequent study.

A more recent paper by Haase et al. helps provide a physiological understanding for why low perfusion flow and pressure are not predictive of postoperative AKI. Their study demonstrates that the combination of low haemoglobin concentration and severe hypotension acted synergistically to increase the risk of AKI.[6] This suggests that low perfusion flow or pressure in isolation may not result in AKI, partly because of the relative reduction in renal oxygen consumption resulting from reduced perfusion and also because of the protective function of haemodilution and hypothermia.[6] This highlights the complexity of CPB-associated AKI and the cumulative effect of individual variables. It is worth noting that the full multivariate model including comprehensive explanatory variables from the registry fails to predict postoperative sCr to any reasonable extent. All variables had some effect but were only able to explain a small amount of variance ($R^2 = 0.061$).

While AKI was the primary outcome of interest in this study, stroke and death were also included because of their close correlation to flow and pressure.[3,23] It is important to consider both renal and cerebral perfusion concurrently, as these provide a greater understanding of the clinical significance of low flow and pressure compared to evaluating single-end-organ perfusion in isolation. Like Slogoff et al., our study did not demonstrate an association between low pressure or flow and stroke or death. However, we suspect that the impact of cerebral dysfunction would be higher if delirium and transient neurological events were included; however, these are undoubtedly harder to standardise for a national registry database. The topic of cerebral perfusion strategy has been debated for many years. There is emerging evidence that individualised targets, using monitoring of cerebral autoregulation, reduces delirium by 45%.[24] However, the Perfusion Pressure Cerebral Infarct Trial will randomise participants on CPB 1:1 to either an increased mean arterial pressure of 70-80 mmHg or 'usual practice (40-50 mmHg)' with the primary outcome being the volume of new ischaemic cerebral lesions.[25] Results are yet to be reported.

Limitations and future studies

We acknowledge that this study is limited by its retrospective nature using registry data. Of note, it is difficult to control for the influence of individual management styles across different centres, surgeons and perfusionists. The study is strengthened by its sample size and duration.

Other limitations of the study include the use of only two sCr measurements and conventional definitions of AKI. In addition, the quantification of low flow may be overestimated in procedures in which it occurred during weaning from CPB, and the period of partial bypass was not documented in the CPB record.

Although blood flow and pressure are important physiological variables, further investigation into their interaction with other factors in AKI is required. The results from this study support a focus on other modifiable factors such as blood conservation and oxygen delivery to reduce AKI following CPB. Future studies could also analyse alternative measure of renal function,

such as urine output, sCr within 2 hours of ICU admission[26] or alternative AKI diagnostic criteria.[13] Further explanatory models such as ischaemic-time analysis may better address the question of cumulative versus consecutive exposure to low flow and pressure. Subset analysis could be considered to evaluate the impact on certain population groups such as diabetic patients.

Conclusion

In conclusion, this binational retrospective cohort study suggests that neither the time spent for perfusion flow (<1.6 L/minute/m^2) nor the time spent for perfusion pressure (<50 mmHg) during CPB was predictive of postoperative AKI, stroke or death.

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Declaration of Conflicting Interests

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Supplemental Material

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References

1. Mazzone AL, Baker RA, Gleadle JM. Mending a broken heart but breaking the kidney. *Nephrology* 2016; 21: 812–820.
2. Ng SY, Sanagou M, Wolfe R, et al. Prediction of acute kidney injury within 30 days of cardiac surgery. *J Thorac Cardiovasc Surg* 2014; 147: 1875–1883.
3. Slogoff S, Reul GJ, Keats AS, et al. Role of perfusion pressure and flow in major organ dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1990; 50: 911–918.
4. Ryden L, Ahnve S, Bell M, et al. Acute kidney injury after coronary artery bypass grafting and long-term risk of myocardial infarction and death. *Int J Cardiol* 2014; 172: 190–195.
5. Kindzelski BA, Corcoran P, Siegenthaler MP, et al. Postoperative acute kidney injury following intraoperative blood product transfusions during cardiac surgery. *Perfusion* 2018; 33: 62–70.
6. Haase M, Bellomo R, Story D, et al. Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on post-operative acute kidney injury. *Nephrol Dial Transplant* 2012; 27: 153–160.
7. Newland RF, Baker RA, Mazzone AL, et al. Rewarming temperature during cardiopulmonary bypass and acute kidney injury: a multicenter analysis presented at the tenth annual perfusion downunder meeting, Queenstown, New Zealand, 6-9 August 2014. *Ann Thorac Surg* 2016; 101: 1655–1662.
8. Newland RF, Baker RA. Low oxygen delivery as a predictor of acute kidney injury during cardiopulmonary bypass. *J Extra Corpor Technol* 2017; 49: 224–230.
9. Newland R, Baker RA, Stanley R, et al. The perfusion Downunder Collaborative Database project. *J Extra Corpor Technol* 2008; 40: 159–165.
10. Newland RF, Baker RA, Barratt CA. Integration of electronic perfusion data for perfusion registries. *J Extra Corpor Technol* 2018; 50: 102–112.
11. The Australian and New Zealand Collaborative Perfusion Registry (ANZCPR). PROTOCOL: the Australian and New Zealand Collaborative Perfusion Registry is a quality improvement initiative, 2016, https://www.anzcpr.org/documents
12. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8: R204–112.
13. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J* 2013; 6: 8–14.
14. Van Biesen W, Vanholder R, Lameire N. Defining acute renal failure: RIFLE and beyond. *Clin J Am Soc Nephrol* 2006; 1: 1314–1319.
15. Kandler K, Jensen ME, Nilsson JC, et al. Arterial pressure during cardiopulmonary bypass is not associated with acute kidney injury. *Acta Anaesthesiol Scand* 2015; 59: 625–631.
16. Thakar CV, Arrigain S, Worley S, et al. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 2005; 16: 162–168.
17. Murphy GS, Hessel EA 2nd, Groom RC. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. *Anesth Analg* 2009; 108: 1394–1417.
18. Sgouralis I, Evans RG, Gardiner BS, et al. Renal hemodynamics, function, and oxygenation during cardiac surgery performed on cardiopulmonary bypass: a modeling study. *Physiol Rep* 2015; 3: 1–14.
19. Bojan M, Basto Duarte MC, Lopez V, et al. Low perfusion pressure is associated with renal tubular injury in infants undergoing cardiac surgery with cardiopulmonary bypass. *Eur J Anaesthesiol* 2018; 35: 581–587.
20. Ono M, Arnaoutakis GJ, Fine DM, et al. Blood pressure excursions below the cerebral autoregulation threshold

during cardiac surgery are associated with acute kidney injury. *Crit Care Med* 2013; 41: 464–471.
21. Fischer UM, Weissenberger WK, Warters RD, et al. Impact of cardiopulmonary bypass management on postcardiac surgery renal function. *Perfusion* 2002; 17: 401–406.
22. Newland R, Baker R, Woodman R, et al. Predictive capacity of oxygen delivery during cardiopulmonary bypass on acute kidney injury. *Ann Thorac Surg* 2019; 108: 1807–1814.
23. Cook DJ, Proper JA, Orszulak TA, et al. Effect of pump flow rate on cerebral blood flow during hypothermic cardiopulmonary bypass in adults. *J Cardiothorac Vasc Anesth* 1997; 11: 415–419.
24. Brown CH 4th, Neufeld KJ, Tian J, et al. Effect of targeting mean arterial pressure during cardiopulmonary bypass by monitoring cerebral autoregulation on postsurgical delirium among older patients: a nested randomized clinical trial. *JAMA Surg* 2019; 154: 819–826.
25. Vedel AG. Perfusion pressure cerebral infarct (PPCI) trial: the importance of mean arterial pressure during cardiopulmonary bypass to prevent cerebral complications after cardiac surgery: study protocol for a randomised controlled trial. *Trials* 2017; 18: 1–11.
26. Grynberg K, Polkinghorne KR, Ford S, et al. Early serum creatinine accurately predicts acute kidney injury post cardiac surgery. *BMC Nephrol* 2017; 18: 93–97.

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Anticoagulation management during pulmonary endarterectomy with cardiopulmonary bypass and deep hypothermic circulatory arrest

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Abstract

Introduction: Pulmonary endarterectomy requires cardiopulmonary bypass and deep hypothermic circulatory arrest, which may prolong the activated clotting time. We investigated whether activated clotting time–guided anticoagulation under these circumstances suppresses hemostatic activation.

Methods: Individual heparin sensitivity was determined by the heparin dose–response test, and anticoagulation was monitored by the activated clotting time and heparin concentration. Perioperative hemostasis was evaluated by thromboelastometry, platelet aggregation, and several plasma coagulation markers.

Results: Eighteen patients were included in this study. During cooling, tube-based activated clotting time increased from 719 (95% confidence interval = 566-872 seconds) to 1,273 (95% confidence interval = 1,136-1,410 seconds; $p < 0.01$) and the cartridge-based activated clotting time increased from 693 (95% confidence interval = 590-796 seconds) to 883 (95% confidence interval = 806-960 seconds; $p < 0.01$), while thrombin–antithrombin showed an eightfold increase. The heparin concentration showed a slightly declining trend during cardiopulmonary bypass. After protamine administration (protamine-to-heparin bolus ratio of 0.82 (0.71-0.90)), more than half of the patients showed an intrinsically activated coagulation test and intrinsically activated coagulation test without heparin effect clotting time >240 seconds. Platelet aggregation through activation of the P2Y12 (adenosine diphosphate test) and thrombin receptor (thrombin receptor activating peptide-6 test) decreased (both −33%) and PF4 levels almost doubled (from 48 (95% confidence interval = 42-53 ng/mL) to 77 (95% confidence interval = 71-82 ng/mL); $p < 0.01$) between weaning from cardiopulmonary bypass and 3 minutes after protamine administration.

Conclusion: This study shows a wide variation in individual heparin sensitivity in patients undergoing pulmonary endarterectomy with deep hypothermic circulatory arrest. Although activated clotting time–guided anticoagulation management may underestimate the level of anticoagulation and consequently result in a less profound inhibition of hemostatic activation, this study lacked power to detect adverse outcomes.

Keywords

heparin; protamine; pulmonary embolism; endarterectomy; cardiopulmonary bypass

Introduction

Incomplete resolution of pulmonary embolism can result in a condition known as chronic thromboembolic pulmonary hypertension (CTEPH), which is characterized by increased pulmonary vascular resistance, pulmonary hypertension, and eventually right heart failure.[1,2] Although the underlying pathophysiological mechanism has not yet been clarified, several risk factors, such as venous thromboembolism, deficiencies of

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antithrombin (AT), excess platelet activation, splenectomy, and pulmonary arteriopathy, have been associated with the development of CTEPH.[1–5]

Pulmonary endarterectomy (PEA) is the surgical treatment for CTEPH and requires cardiopulmonary bypass (CPB) with deep hypothermic circulatory arrest (DHCA).[1,2,6] Unfractionated heparin is administered to prevent thrombin generation due to continuous exposure of circulating blood to the non-biological surfaces of the CPB circuit and recirculation of mediastinal shed blood through cardiotomy suction.[7,8] Studies by Bull et al.[9,10]and Young et al.[11] in the 1970s are considered groundbreaking in the quest for a tailored approach to anticoagulation management during CPB, which continues to today. Based on their research, the anticoagulant effect of heparin is still monitored by the activated clotting time (ACT), even though this test is concomitantly influenced by hemodilution and hypothermia, potentially resulting in lower levels of anticoagulation.[12–15]

Since the majority of CTEPH patients show a thrombogenic hemostasis profile,[1–5] this may increase their risk for thrombotic and/or bleeding complications even further. The aim of this explorative study was to investigate whether ACT-guided anticoagulation management during PEA with CPB and deep hypothermia suppresses hemostatic activation in CTEPH patients. The heparin dose–response (HDR) test was used to identify patients with reduced sensitivity to heparin.[16–18]

Methods

Study population and design

This prospective, explorative clinical study was performed by the Departments of Cardio-Thoracic Surgery and Anesthesiology of the Amsterdam University Medical Centre (VU University Amsterdam, The Netherlands). The protocol was approved by the Human Subjects Committee of our institution (PTE; NL54265.029.15). All eligible patients provided written informed consent. Patients aged between 18 and 85 years were eligible in case of elective PEA. The exclusion criterion was re-operation. All patients stopped oral anticoagulation a week prior to surgery and were bridged with subcutaneous low-molecular-weight heparin. Blood samples for hemostatic measurements and laboratory testing were collected from a radial artery catheter at the following time points and corresponding body temperatures: (0) upon induction of anesthesia (baseline), (1) after initiating CPB (T_{rectal} = 35°C), (2) at moderate hypothermia (Cooling I, T_{rectal} = 30°C), (3) before initiating circulatory arrest (Cooling II, T_{rectal} = 20°C), (4) after initiating rewarming (Warming I, T_{rectal} = 20°C), (5) at moderate hypothermia (Warming II, T_{rectal} = 30°C), (6) just before weaning of CPB (T_{rectal} = 35°C), and (7) 3 and (8) 30 minutes after protamine administration. Blood was centrifuged, and platelet-free plasma was extracted and stored at −80°C for further analysis.

Anesthesia

Anesthesia was induced using sufentanyl, rocuronium, diazepam, or midazolam, followed by continuous infusion of propofol, dopamine, and inhalation of isoflurane. After induction, systemic cooling with both a head jacket and a blanket was initiated. Cerebral saturation by near-infrared spectroscopy (Foresight®, CAS Medical Systems, Inc.), mean arterial pressure (radial artery and femoral artery), pulmonary artery pressure (PA catheter), and cardiac output and temperature (skin, rectal, bladder, and nasopharyngeal) were continuously monitored.

CPB

CPB during PEA was performed using a C5 heart-lung machine (Stöckert Instrumente GmbH, Munich, Germany) with a disposable, phosphorylcholine-coated extracorporeal circuit (Sorin Group, Mirandola, Italy), which consists of a polyvinyl tubing system, an oxygenator with integrated arterial filter (Inspire 6), a soft shell collapsible venous reservoir, centrifugal pump (Revolution), and heater-cooler device (Stöckert Instrumente GmbH). The circuit was primed with 600 mL of modified fluid gelatin (Braun Melsungen AG, Melsungen, Germany), 500 mL of lactated Ringer's solution (Baxter BV, Utrecht, The Netherlands), 200 mL of mannitol (15%; Baxter BV), 100 mL of sodium bicarbonate (8.4%; Braun Melsungen AG) and 5,000 IU of heparin. Additional fluids during CPB (albumin, 200 g/L; Sanquin, Leiden, The Netherlands) and lactated Ringer's solution (Baxter BV) were administered in a 1:5 ratio. After initiating CPB, the patient was gradually cooled to a rectal temperature of 18-20°C. Crystalloid cardioplegia (modified St. Thomas) was used to achieve cardiac arrest and additional myocardial protection was offered by wrapping a cooling jacket around the heart. After two to four circulatory stops for PEA and removal of the aortic clamp, the patient was gradually rewarmed to a core temperature of 35.5°C. Prior to weaning from CPB, every patient underwent bronchoscopy for endobronchial bleeding. If profuse bleeding was present, a bronchial blockade was placed.

Anticoagulation management and monitoring

The hemostasis management system (Hepcon HMS; Medtronic, Minneapolis, MN, USA) was used to perform

the HDR test to determine the individual response to heparin, thereby identifying patients with reduced sensitivity to heparin (HDR slope < 80 seconds/IU/mL).[16–18] The individual target heparin concentration, to reach a target ACT of 480 seconds, was also calculated based on the HDR slope and compared with the measured whole blood heparin concentration (heparin-protamine titration (HPT) test). Since the HPT test contains thromboplastin, prewarming to 37°C is not necessary and the test remains reliable under conditions of hypothermia and hemodilution. These measurements were for research purposes only.

The ACT (tube-based Hemochron® Response and the cuvette-based Hemochron® Signature Elite; Werfen Benelux, Breda, The Netherlands) was measured to monitor the periprocedural degree of anticoagulation. Heparin management during PEA was guided by the tube-based ACT. Prior to arterial cannulation, an initial bolus of 400 IU/kg unfractionated porcine heparin (LEO Pharma BV, Amsterdam, The Netherlands) was administered to achieve a target ACT of 480 seconds. Additional doses (5,000 IU) of heparin were given to maintain an ACT ⩾480 seconds during CPB, during cooling and rewarming at $T_{rectal} = 30°C$, and before initiating circulatory arrest. After weaning from CPB, the total dose of heparin was reversed with protamine hydrochloride (MedaPharma BV, Amstelveen, The Netherlands) in a protamine-to-heparin ratio of 0.8 based on the initial heparin bolus.

Monitoring hemostasis

The viscoelastic properties of a clot in whole blood were assessed by rotational thromboelastometry (ROTEM delta; TEM International GmbH, Munich, Germany), which included the intrinsically activated coagulation test (INTEM), the extrinsically activated coagulation test (EXTEM), the fibrin polymerization test (FIBTEM), and the intrinsically activated coagulation test without heparin effect (HEPTEM). The Multiplate® analyzer (Roche Diagnostics Nederland BV) was used to assess platelet function by adding the potent platelet activator adenosine diphosphate (ADP test, final concentration of 6.5 µM ADP) or thrombin receptor activating peptide-6 (TRAP test, final concentration of 32 µM TRAP-6) to whole blood. Routine laboratory testing of the international normalized ratio (INR) of the prothrombin time (calcium thromboplastin) and activated partial thromboplastin time (aPTT; cefaline) was determined using an STA-R instrument® (Roche Diagnostics FmbH, Basel, Switzerland) in platelet-free plasma. Other hemostatic parameters included hemoglobin and hematocrit levels and platelet count. AT, thrombin–antithrombin complex (TAT), and prothrombin fragment 1 + 2 (F1 + 2) were determined using a chromogenic assay (Werfen Benelux), while platelet factor 4 (PF4) was determined by ELISA (R&D systems). Finally, citrated platelet-free plasma was analyzed with calibrated automated thrombography (CAT) to assess thrombin generation.[19] This assay was only performed at baseline (T0) and after administering protamine, since heparin can interfere with this measurement.

Other study parameters

Patient demographics included age, gender, and body mass index (BMI). Surgical data included the duration of CPB, aortic cross-clamp, circulatory arrest, and the dose of heparin and protamine that was administered. Clinical outcomes such as myocardial infarction (MI), transient ischemic attack (TIA), cerebral vascular incident (CVA), cardiac tamponade, re-explorations, and bleeding complications were also assessed.

Statistical analysis

The primary study endpoint was the level of periprocedural anticoagulation as measured by heparin concentration and the ACT. Statistical analysis was performed using SPSS statistical software package 23.0 (IBM, New York, USA) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA). Distribution of data was tested for normality using the Shapiro–Wilk test, normally distributed variables were expressed as mean with 95% confidence interval (95% CI), while skewed and ordinal data were shown as median with interquartile range [IQR]. Two-sided paired t-test or Wilcoxon signed-rank test was used to evaluate differences between time points. Differences over time were analyzed using linear mixed models with Bonferroni post hoc analyses. Categorical variables were expressed as frequencies and analyzed using the chi-square test. A value of $p \leqslant 0.05$ was considered as statistically significant.

Results

Of the 19 patients included in this study, one patient was excluded from further analysis due to abnormal preoperative aPTT and INR values. Table 1 describes the preoperative and procedural characteristics of the patient population. Two out of three patients were male and 72% of the study population had a history of recurrent pulmonary embolism. Patients showed a wide variation in individual heparin sensitivity, ranging from 50 to 120 seconds/IU/mL, as determined by the HDR test.

Anticoagulation monitoring

Figure 1 shows that cooling increased the tube-based ACT (from 719 (95% CI = 566-872 seconds) to 1,273

Table 1. Preoperative and procedural characteristics.

N	18
Age (years)	67 [62-71]
BMI (kg/m^2)	26 (24-28)
Males (n (%))	12 (67)
Recurrent PE (n (%))	13 (72)
DVT (n (%))	4 (22)
Splenectomy (n (%))	1 (6)
Baseline hemostatic tests	
Platelet count (10^9/L)	262 (229-294)
Hematocrit (%)	47 (45-48)
aPTT (seconds)	37 (35-40)
INR	1.06 [1.02-1.08]
AT (μg/mL)	144 (128-159)
CPB duration (minutes)	340 (321-360)
Aortic cross-clamp duration (minutes)	141 (124-158)
Circulatory arrest duration (minutes)	50 (43-57)
Circulatory arrests (n)	3 [2-3]
Heparin slope (seconds/IU/mL)	69 [56-86]
Heparin bolus (mg)	325 [300-400]
Heparin during CPB (mg)	200 [150-250]
Total heparin (mg)	525 [450-600]
Total protamine (mg)	263 [225-300]
Protamine-to-heparin bolus ratio	0.82 [0.71-0.90]

BMI: body mass index; PE: pulmonary embolism; DVT: deep vein thrombosis; CPB: cardiopulmonary bypass, aPTT: activated partial thromboplastin time, INR: international normalized ratio, AT: antithrombin.
Data represent frequencies (n (%)), means (95% CI), or median [interquartile range].

(95% CI = 1,136-1,410 seconds); $p < 0.01$) and the cartridge-based ACT (from 693 (95% CI = 590-796 seconds) to 883 (95% CI = 806-960 seconds); $p < 0.01$). During rewarming, ACT values decreased in both the tube-based ACT (from 1,042 (95% CI = 855-1,228 seconds) to 710 (95% CI = 561-860 seconds); $p < 0.01$) and the cartridge-based ACT (from 842 (95% CI = 742-942 seconds) to 588 (95% CI = 525-651 seconds); $p < 0.01$). The measured heparin concentration remained lower than the calculated target heparin concentration during CPB (Figure 1, panel (c); F-value = 114.79; $p < 0.01$) and showed a slightly declining trend over time.

Hemostasis monitoring

Figure 2 shows the clotting time (CT) and clot formation time (CFT) for the INTEM, HEPTEM, and platelet aggregation (area under the curve (AUC)) in the ADP and TRAP test. Between weaning from CPB and 3 minutes after protamine administration, both the HEPTEM CT (panel (a); 209 (95% CI = 195-223 seconds) vs. 279 (95% CI = 227-330 seconds); $p < 0.05$) and HEPTEM CFT (panel (b); 151 (95% CI = 126-177 seconds) vs. 190 (95% CI = 136-243 seconds); $p < 0.05$) were prolonged. The INTEM CT (panel (c); 281 (95% CI = 236-325 seconds)) and the INTEM CFT (panel (d); 187 (95% CI = 135-240 seconds)) showed comparable values after protamine.

During cooling, platelet count decreased from 162 (95% CI = 184-140 × 10^9/L) to 78 (95% CI = 90-66 × 10^9/L) and was only partially recovered toward the end of CPB (107 (95% CI = 126-88 × 10^9/L)). Platelet aggregation decreased during cooling and increased during rewarming, but did not fully recover toward the end of CPB. After protamine, platelet aggregation decreased in the ADP test (panel (e); 43 (95% CI = 34-52 U vs. 29 (95% CI = 20-37 U); $p < 0.01$) and in the TRAP test (panel (b); 90 (95% CI = 72-107 U vs. 60 (95% CI = 48-72 U); $p < 0.01$).

Between initiating CPB and rewarming (Warming I), TAT levels increased (Figure 3, panel (a); 12 (95% CI = 8-16 ng/mL) vs. 95 (95% CI = 53-137 ng/mL); $p < 0.01$), while AT levels decreased by 66% compared to baseline levels (144 (95% CI = 128-159 μg/mL) vs. 49 (95% CI = 47-50 μg/mL); $p < 0.01$). PF4 levels almost doubled between weaning from CPB and 3 minutes after protamine (Figure 3, panel (b); 48 (95% CI = 42-53 ng/mL) vs. 77 (95% CI = 71-82 ng/mL); $p < 0.01$). Almost 40% of the study population showed elevated F1 + 2 levels (>250 pg/mL) at baseline (Figure 3, panel (c)).

Thrombin generation assay

Figure 4 shows the normalized values (% relative to normal pooled plasma) for the thrombin generation assay at baseline and 3 and 30 minutes after protamine. Compared to baseline values, the lag time (panel (a); F-value = 27.75; $p < 0.01$) and the time to peak (TT peak, panel (d); F-value = 13.04; $p < 0.01$) increased, while peak height (panel (b); F-value = 18.188; $p < 0.01$) and endogenous thrombin potential (ETP, panel (c); F-value = 20.50; $p < 0.01$) decreased after protamine.

Intraoperative complications and blood transfusion

Table 2 describes the postoperative characteristics of the patient population. Bronchoscopy revealed pulmonary bleeding in one patient, which was managed by adjusting ventilation parameters and stopped with administration of protamine. Thrombocytes (1 U) and fibrinogen (2 g) were administered to one patient, while two other patients received prothrombin complex concentrate (250 and 500 IU, respectively). Two other patients received packed red cells (3 U). Infusion of cell-saved blood during and post-CPB was 238 [0-432] mL and 598 [492-761] mL, respectively. Postoperative blood loss at 12 hours was 135 [94-205] mL.

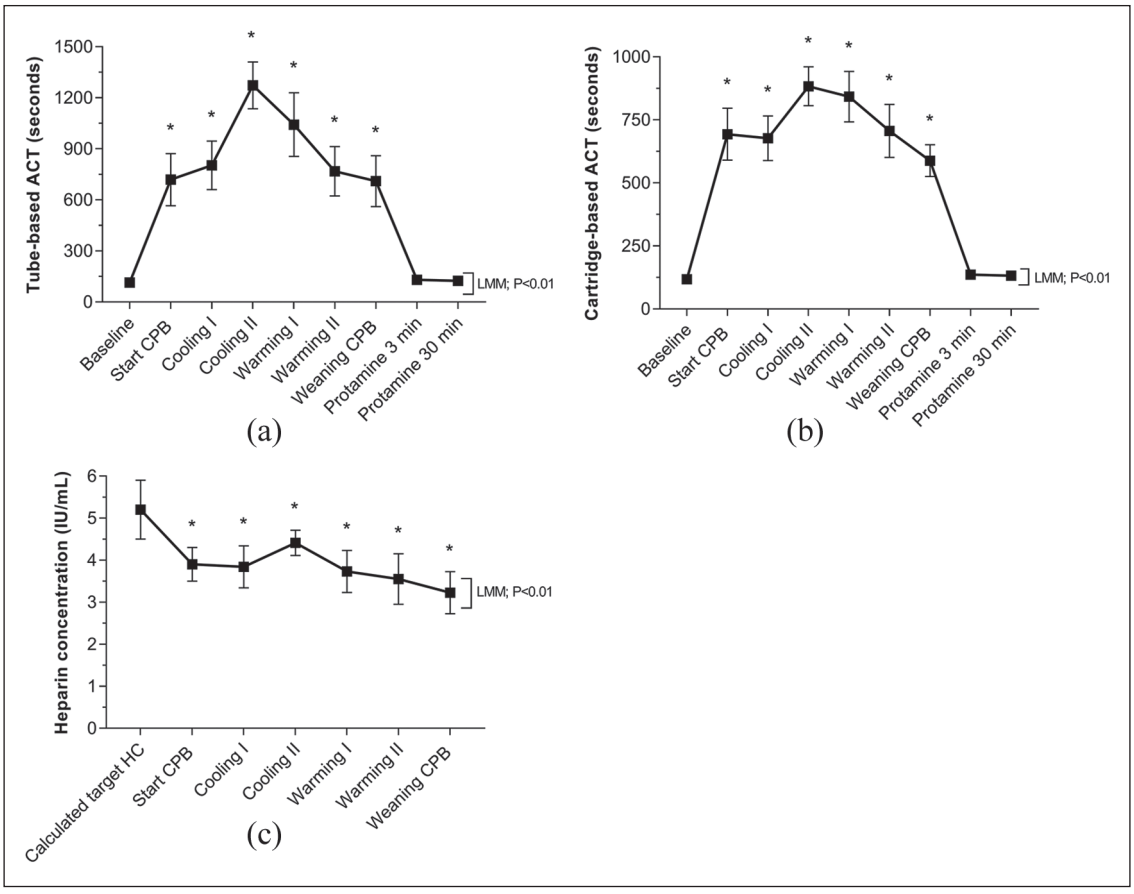

Figure 1. Intraoperative values for the activated clotting time (ACT) measured with (a) a tube-based (Hemochron® Response) or (b) a cartridge-based (Hemochron® Signature Elite) point-of-care system, and (c) heparin concentration in patients undergoing pulmonary endarterectomy (PEA). Data represent means (95% CI) and are analyzed using linear mixed models (LMM) with Bonferroni post hoc analyses.
*$p < 0.05$ versus baseline, calculated target heparin concentration.

Discussion

This study shows that ACT-guided anticoagulation management resulted in heparin concentrations below the calculated required individual target heparin concentration in PEA patients. TAT levels increased during hypothermia, while PF4 and F1 + 2 levels increased during rewarming, despite prolonged ACT values in both the tube-based and the cartridge-based tests. Incomplete inhibition of hemostatic activation could potentially increase their risk for perioperative thrombotic and/or bleeding complications, especially since patients undergoing PEA may have an altered hemostatic profile.[1–5]

Individual heparin sensitivity varies widely in patients undergoing cardiac surgery.[9,16,17] Several factors have been identified that could affect the individual heparin sensitivity, such as thrombocytosis, high levels of PF4, its non-specific binding to macrophages, platelets and endothelial cells, and low AT levels.[13,16–18] Our study reveals that patients undergoing PEA do not necessarily show a reduced heparin sensitivity, but patients with reduced heparin sensitivity more frequently reveal thrombocytosis. The concomitant elevated preoperative PF4 levels could be the result of excessive platelet aggregation, which has been frequently described in patients with CTEPH.[4,5] Since PF4 has a strong binding affinity for negatively charged glycosaminoglycans, such as heparin,[20] this could at least partly contribute to the declining trend in heparin concentration during CPB. Finally, AT levels below the normal range (125-160 µg/mL) could also reduce the anticoagulant effect of heparin.[21] Almost one of three patients showed AT levels <125 µg/mL, but this did not particularly associate with higher levels of hemostatic activation during CPB compared to patients with normal AT levels.

ACT-guided anticoagulation management is still considered the gold standard during CPB.[12–15] However, low levels of coagulation factors and platelets, hemodilution, and hypothermia may prolong the ACT during CPB, potentially resulting in lower levels of anticoagulation

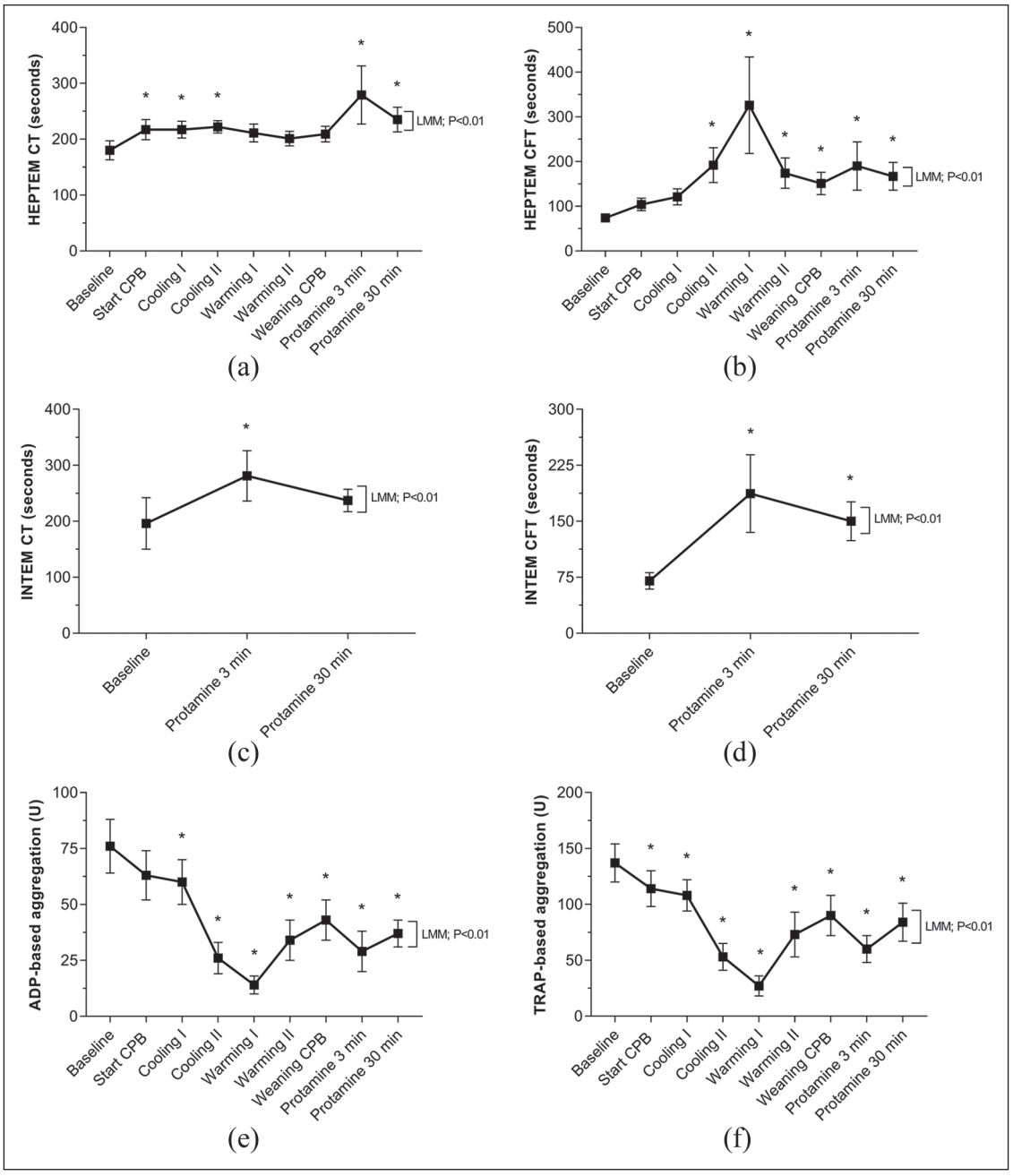

Figure 2. Intraoperative values for rotational thromboelastometry parameters (a) HEPTEM CT, (b) HEPTEM CFT, (c) INTEM CT, and (d) INTEM CFT; (e) adenosine diphosphate (ADP test)–based platelet aggregation; and (f) thrombin receptor activating peptide-6 (TRAP test)–based platelet aggregation in patients undergoing pulmonary endarterectomy (PEA). Data represent means (95% CI) and are analyzed using linear mixed models (LMM) with Bonferroni post hoc analyses.
*$p < 0.05$ versus baseline.

in the patient.[12–15] Previously, Shirota and others studied the effect of deep and moderate hypothermia on anticoagulation management in patients undergoing cardiac surgery, which was guided by measuring either the ACT or the heparin concentration. During deep hypothermia, the measured heparin concentration was reduced by half compared to the initial heparin concentration in the ACT group, despite ACT values that had almost doubled.[22] This study shows a comparable trend for the ACT, but not for the heparin concentration that only slightly declined over time, the latter most likely caused by additional heparin doses that were administered during PEA despite ACT values ⩾480 seconds as a safety window, since the optimal heparin level is unknown for this specific patient population. TAT levels sharply increased during cooling and remained higher than

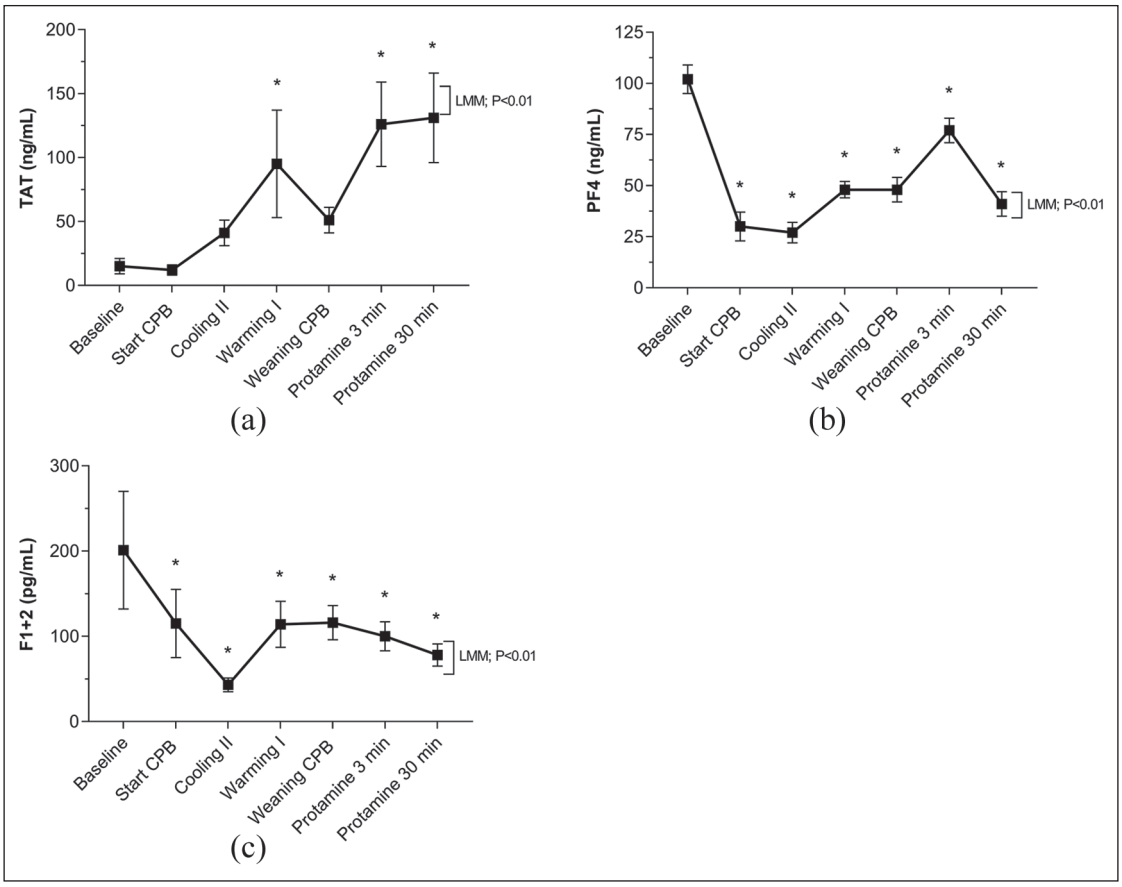

Figure 3. Intraoperative values for plasma coagulation markers in patients undergoing pulmonary endarterectomy (PEA). (a) Thrombin–antithrombin complex (TAT), (b) platelet factor 4 (PF4), and (c) prothrombin fragment 1 + 2 (F1 + 2). Data represent means (95% CI) and are analyzed using linear mixed models (LMM) with Bonferroni post hoc analyses.
*$p < 0.05$ versus baseline.

baseline levels just before weaning from CPB, which may be the result of suboptimal levels of anticoagulation. The exposure of circulating blood to the non-biological surfaces of the CPB circuit and reinfusion of aspirated highly thrombogenic blood from the pericardial and pleural cavities both contribute to continuous thrombin generation during CPB.[7,8] However, during PEA, blood from these cavities was aspirated and processed through cell salvage prior to reinfusion to minimize its thrombogenic potential.

We used a tube-based and cartridge-based point-of-care ACT device that differs in terms of clot detection and sample volume. The measuring principle of the Hemochron Response device is based on the specific displacement of a magnet as soon as fibrin clot formation occurs, whereas the Hemochron Signature Elite measures the rate of blood movement in a cuvette, which will decrease with clot formation. The latter only requires a sample volume of 0.015 mL instead of 2 mL, thereby decreasing the prewarming phase to 37°C, potentially making it less affected by hypothermia. However, our study shows that during hypothermia the number of ACT measurements that were out of range (Hemochron Response >1,500 seconds and Hemochron Signature Elite >1,000 seconds) increased from 11% up to 56% in both devices. Although these values suggest high levels of anticoagulation, the measured heparin concentration was below the calculated target heparin concentration in the majority of patients throughout CPB, potentially underestimating the anticoagulation status.

All patients received an initial heparin bolus of 400 IU/kg, with a half-life of approximately 150 minutes, although deep hypothermia could prolong this half-life because the slower unsaturable clearance of heparin is largely renal.[23] Since the duration of CPB during PEA exceeded 300 minutes in almost all patients, it is very unlikely that the remaining quantity could completely suppress hemostatic activation. This was reflected by decreasing heparin levels during rewarming in all patients despite additional doses of heparin at fixed time points. ACT values, however, remained prolonged during this phase, thus poorly reflecting the anticoagulant effect of heparin.

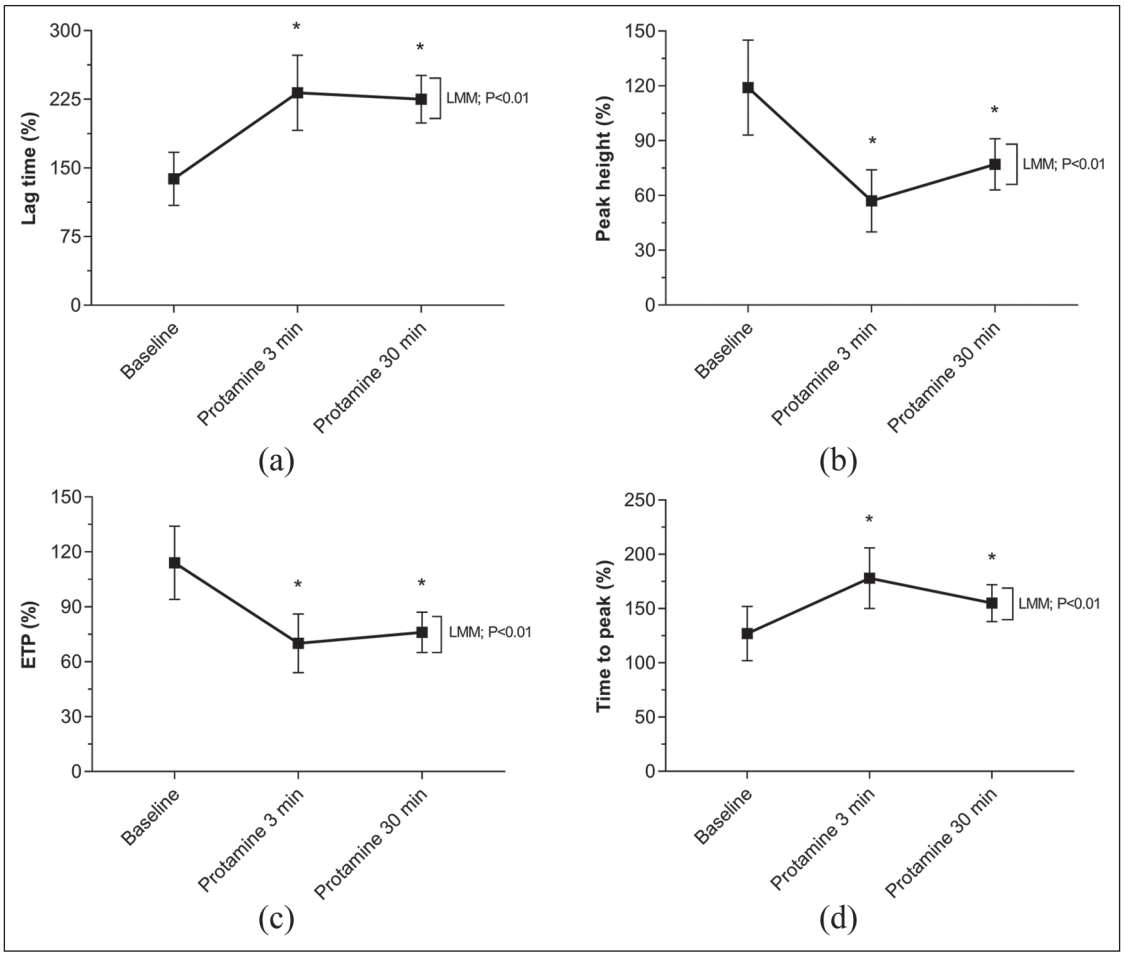

Figure 4. Intraoperative normalized values (% relative to normal pooled plasma) for thrombin generation parameters in patients undergoing pulmonary endarterectomy (PEA). (a) Lag time, (b) peak height, (c) endogenous thrombin generation potential, and (d) time to peak thrombin (TT peak). Data represent means (95% CI) and are analyzed using linear mixed models (LMM) with Bonferroni post hoc analyses.
*$p < 0.05$ versus baseline.

Deep hypothermia during PEA is mandatory to achieve an optimal cerebral and myocardial protection and a bloodless operation field, thereby enabling the surgeon to remove the organized blood clots from the pulmonary arteries.[6,24] Hypothermia may decelerate the enzymatic activity of coagulation factors, enhance shear-induced platelet aggregation by increasing blood viscosity, and induce thrombocytopenia through hepatic and splenic sequestration.[25,26] We indeed found a platelet count drop by 50% during deep hypothermia. Others showed that moderate hypothermia induced a pronounced prolongation of clot initiation and formation in rotational thromboelastometry, whereas we only found the latter to be affected by temperature, in particular during DHCA.[27] Their study, however, was performed with blood of healthy volunteers without a history of coagulation disorders, while our study included patients who could potentially be hypercoagulable and who were subjected to CPB with consequent hemodilution. Ortman and others showed that DHCA severely inhibited platelet aggregation that partially recovered during rewarming, which is in accordance with the present findings.[28] In addition, we also activated platelets via the ADP receptor (ADP test), but the trend over time was comparable. Hence, the effect of hypothermia on platelet aggregation seemed to be receptor-independent.

After weaning from CPB, heparin is routinely reversed by administrating protamine sulfate, a highly cationic polypeptide. However, protamine may exert a detrimental effect on postoperative hemostasis when it is administered in excess of heparin.[28–31] This study shows a substantial decrease in platelet aggregation through activation of P2Y12 (ADP test) and thrombin receptor (TRAP test), which is line with previous studies.[28–30] Interestingly, we also showed a doubling of PF4 levels, confirming protamine-induced platelet activation. The optimal protamine-to-heparin ratio in PEA,

Table 2. Postoperative characteristics.

Cell-saved blood during CPB (mL)	238 [0-432]
Cell-saved blood post-CPB (mL)	598 [492-761]
12-hour blood loss (mL)	135 [94-205]
Ventilation duration (hours)	28 [19-63]
ICU duration (hours)	94 [50-147]
Transfusion blood products	
Packed red cells (U)	0 [0-0]
Platelets (U)	0 [0-0]
Fresh frozen plasma (U)	0 [0-0]
Prothrombin complex concentrate (IU)	0 [0-0]
Fibrinogen (g)	0 [0-0]
Complications	
Pulmonary bleeding	1 (6)
Re-exploration (n (%))	1 (6)
In-hospital death (n (%))	1 (6)
Myocardial infarction (n (%))	0 (0)
Transient ischemic attack (n (%))	0 (0)
Cerebral vascular incident (n (%))	0 (0)

ICU = intensive care unit.
Data represent frequencies (n (%)) or median [interquartile range].

and cardiac surgery in general, remains unknown and may vary between 0.6 and 1.0 based on the initial heparin dose.[31,32]

Study limitations

This prospective study was intended to gain more insight into anticoagulation management and hemostatic risk in patients undergoing pulmonary thromboendarterectomy with CPB during DHCA. The generalizability of our findings and the ability to identify adverse events are automatically limited by our relatively small cohort with a single-center design.

The heparin concentration, as measured by the cartridge-based HPT test, is based on clot formation as a surrogate endpoint and therefore does not reflect the exact heparin concentration. Moreover, a resolution of 0.7 IU/mL exists between the channels, thereby influencing the accuracy of this test, for example, a measured heparin concentration of 4.1 IU/mL could be between 3.7 and 4.4 IU/mL. On the contrary, these values correlate well with laboratory anti-Xa values, in contrast to ACT values that show a poor correlation during CPB.[12–14]

Nevertheless, our findings may question the idea that ACT-guided anticoagulation management under these conditions should remain the gold standard, which is also in line with the recent guidelines on patient blood management for adult cardiac surgery.[29]

Conclusion

In conclusion, this study shows a wide variation in individual heparin sensitivity in patients undergoing PEA. Moreover, ACT-guided anticoagulation management during PEA with DHCA may underestimate the level of anticoagulation and consequently result in a less profound inhibition of hemostatic activation, thus increasing their risk for thrombotic and/or bleeding complications, in particular during the rewarming phase. Large multicenter, randomized clinical studies should explore the added value of individualized heparin and protamine management, since the majority of this specific patient population has an altered hemostatic profile.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Banks DA, Pretorius GV, Kerr KM, et al. Pulmonary endarterectomy: Part I. Pathophysiology, clinical manifestations, and diagnostic evaluation of chronic thromboembolic pulmonary hypertension. *Semin Cardiothorac Vasc Anesth* 2014; 18: 319–330.
2. Klok FA, Huisman MV. Epidemiology and management of chronic thromboembolic pulmonary hypertension. *Neth J Med* 2010; 68: 347–351.
3. Lang IM, Dorfmüller P, Vonk Noordegraaf A. The pathobiology of chronic thromboembolic pulmonary hypertension. *Ann Am Thorac Soc* 2016; 13: S215–S221.
4. Lannan KL, Phipps RP, White RJ. Thrombosis, platelets, microparticles and PAH: more than a clot. *Drug Discov Today* 2014; 19: 1230–1235.
5. Yaoita N, Shirakawa R, Fukumoto Y, et al. Platelets are highly activated in patients of chronic thromboembolic pulmonary hypertension. *Arterioscler Thromb Vasc Biol* 2014; 34: 2486–2494.
6. Banks DA, Pretorius GV, Kerr KM, et al. Pulmonary endarterectomy: Part II. Operation, anesthetic management, and postoperative care. *Semin Cardiothorac Vasc Anesth* 2014; 18: 331–340.
7. Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. *Anesth Analg* 2011; 113: 1319–1333.
8. Weerwind PW, Lindhout T, Caberg NE, et al. Thrombin generation during cardiopulmonary bypass: the possible role of retransfusion of blood aspirated from the surgical field. *Thromb J* 2003; 1: 3.
9. Bull BS, Korpman RA, Huse WM, et al. Heparin therapy during extracorporeal circulation. I. Problems inherent in existing heparin protocols. *J Thorac Cardiovasc Surg* 1975; 69: 674–684.

10. Bull BS, Huse WM, Brauer FS, et al. Heparin therapy during extracorporeal circulation. II. The use of a dose-response curve to individualize heparin and protamine dosage. *J Thorac Cardiovasc Surg* 1975; 69: 685–689.
11. Young JA, Kisker CT, Doty DB. Adequate anticoagulation during cardiopulmonary bypass determined by activated clotting time and the appearance of fibrin monomer. *Ann Thorac Surg* 1978; 26: 231–240.
12. Lander H, Zammert M, FitzGerald D. Anticoagulation management during cross-clamping and bypass. *Best Pract Res Clin Anaesthesiol* 2016; 30: 359–370.
13. Sniecinski RM, Levy JH. Anticoagulation management associated with extracorporeal circulation. *Best Pract Res Clin Anaesthesiol* 2015; 29: 189–202.
14. Shore-Lesserson L. Evidence based coagulation monitors: heparin monitoring, thromboelastography, and platelet function. *Semin Cardiothorac Vasc Anesth* 2005; 9: 41–52.
15. Bosch YP, Weerwind PW, Nelemans PJ, et al. An evaluation of factors affecting activated coagulation time. *J Cardiothorac Vasc Anesth* 2012; 26: 563–568.
16. Finley A, Greenberg C. Review article: heparin sensitivity and resistance: management during cardiopulmonary bypass. *Anesth Analg* 2013; 116: 1210–1222.
17. Despotis GY, Avidany M, Levy JH. Heparin resistance and the potential impact on maintenance of therapeutic coagulation. *Eur J Anaesth* 2007; 24: S37–S58.
18. Vuylsteke A, Mills RJ, Crosbie AE, et al. Increased preoperative platelet counts are a possible predictor for reduced sensitivity to heparin. *Br J Anaesth* 2000; 85: 896–898.
19. Hemker HC, Giesen P, Al Dieri R, et al. Calibrated automated thrombin generation measurement in clotting plasma. *Pathophysiol Haemost Thromb* 2003; 33: 4–15.
20. Kowalska MA, Rauova L and Poncz M. Role of the platelet chemokine platelet factor 4 (PF4) in hemostasis and thrombosis. *Thromb Res* 2010; 125: 292–296.
21. Levy JH, Sniecinski RM, Welsby IJ, et al. Antithrombin: anti-inflammatory properties and clinical applications. *Thromb Haemost* 2016; 115: 712–728.
22. Shirota K, Watanabe T, Takagi Y, et al. Maintenance of blood heparin concentration rather than activated clotting time better preserves the coagulation system in hypothermic cardiopulmonary bypass. *Artif Organs* 2000; 24: 49–56.
23. Hirsh J, Bauer KA, Donati MB, et al. Parenteral anticoagulants: American college of chest physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008; 133: 141S–159S.
24. Campos JM, Paniagua P. Hypothermia during cardiac surgery. *Best Pract Res Clin Anaesthesiol* 2008; 22: 695–709.
25. Van Poucke S, Stevens K, Marcus AE, et al. Hypothermia: effects on platelet function and hemostasis. *Thromb J* 2014; 12: 31.
26. Wolberg AS, Meng ZH, Monroe DM III, et al. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *J Trauma* 2004; 56: 1221–1228.
27. Rundgren M, Engström M. A thromboelastometric evaluation of the effects of hypothermia on the coagulation system. *Anesth Analg* 2008; 107: 1465–1468.
28. Ortmann E, Klein AA, Sharples LD, et al. Point-of-care assessment of hypothermia and protamine-induced platelet dysfunction with multiple electrode aggregometry (Multiplate®) in patients undergoing cardiopulmonary bypass. *Anesth Analg* 2013; 116: 533–540.
29. Mochizuki T, Olson PJ, Szlam F, et al. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. *Anesth Analg* 1998; 87: 781–785.
30. Olsson A, Alfredsson J, Håkansson E, et al. Protamine reduces whole blood platelet aggregation after cardiopulmonary bypass. *Scand Cardiovasc J* 2016; 50: 58–63.
31. Boer C, Meesters MI, Veerhoek D, et al. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. *Br J Anaesth* 2018; 120: 914–927.
32. Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) the European Association of Cardiothoracic Anaesthesiology (EACTA)Boer C, Meesters MI, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth* 2018; 32: 88–120.

Case Report

Perfusion

Perfusion
2021, Vol. 36(1) 97–99

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Air in extracorporeal membrane oxygenation: can never be overemphasized

Shujie Yan,[1] Song Lou,[1] Yu Zhao,[2] Gang Liu[1] and Bingyang Ji[1]

Abstract

Introduction: Air in extracorporeal membrane oxygenation circuit may lead to deleterious consequence.

Case report: Three cases of air in extracorporeal membrane oxygenation were presented. Air was introduced from right jugular venous sheath during percutaneous septal repair, pulmonary artery catheter during intensive care unit, and sewing holes on atrial wall during surgery respectively. Accidents in Case 2 and Case 3 were successfully managed, while Case 1 was suspected of cerebral air embolism through transseptal right-to-left shunt.

Discussion: With extracorporeal membrane oxygenation being widely applied in more clinical settings, especially in catheterization lab, risks of air in extracorporeal membrane oxygenation increase. More attention should be paid to patients with communication between right and left heart system, especially in situations when venous accesses' exposure to air could not be avoided.

Conclusion: Air in the extracorporeal membrane oxygenation circuit should never be overemphasized, especially during special procedures.

Keywords

extracorporeal membrane oxygenation; air in ECMO circuit; percutaneous septal repair; catheter interventions; accident during ECMO

Introduction

Air in extracorporeal membrane oxygenation (ECMO) circuit may lead to deleterious consequence, either by tripping the pump or causing air embolism. As venoarterial ECMO is applied with extended indications and more complex interventions are performed on ECMO,[1] risks increased. Here we present three typical cases we encountered recently. Our institutional review board approved the case reports and waived the need for informed consent.

Case report

Case 1

A 79-year-old man was admitted with diagnosis of acute anterior-inferior-wall infarction, post-infarction ventricular septal defects, and cardiogenic shock. Considering high-surgery risk, multidisciplinary team decided to do percutaneous septal closure and coronary angioplasty on ECMO. ECMO was cannulated via right femoral vein and left femoral artery. After full flow (3,500 mL/min) was achieved, percutaneous septal repair was started via right jugular vein and right femoral artery. During the procedure, massive air was seen returning into venous line and oxygenator. Arterial line was clamped immediately, pump was stopped, and air was expelled through oxygenator. Air was considered introduced from right jugular venous sheath by negative pressure. To avoid more air in, pump speed was maintained below 2000 r/min until septal repair was completed. Hemodynamic parameters and circuit were closely monitored. De-air was performed twice subsequently. No visible air bubbles entered arterial line during entire procedure. Then, coronary stenting was performed via right brachial artery.

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Table 1. Protocol for air in ECMO circuit.

Prevention
General management
1. An air detector is recommended on the circuit
2. Venous access should be checked at intervals (venous accesses include, but are not limited to peripheral intravenous infusion lines, peripherally inserted central catheters, central venous catheters, and pulmonary artery catheters)
3. Any manipulation on venous accesses should be careful
4. In case of insufficient venous return, to achieve satisfactory flow by increasing ECMO speed is not recommended
If venous access exposure to air cannot be avoided during certain procedures
1. Stop or speed down the pump temporarily
2. Patients in Trendelenburg position
3. Monitor the circuit closely and expel air timely
Treatment
1. Clamp the arterial line and turn off the pump
2. Expel the air from circuit
3. Check all the venous access and find out air-inlet
4. Resume the circuit
5. (If air entering arterial line) neuroprotection strategies (hypothermia, steroids, mannitol, etc.), FiO2 100%, hyperbaric oxygenation

ECMO: extracorporeal membrane oxygenation

However, after the procedures, the patient gradually developed progressive conscious disturbance. Although he was weaned from ECMO with cardiac function recovered after 7 days, he did not survive because of irreversible brain injury. Brain injury was considered might be related to cerebral air embolism through ventricular septal right-to-left shunt. Brain image was not performed to confirm the diagnosis.

Case 2

A 17-year-old man diagnosed with hypertrophic cardiomyopathy underwent heart transplantation. Femoral venoarterial ECMO (3,300 L/min, 2900 r/min) was implanted postoperatively because of primary graft failure. On the third day, continuous air bubbles were noticed entering the venous line. Arterial line was clamped, and air was expelled. Careful examination of all the venous accesses revealed that air came from an incompletely closed stopcock on pulmonary artery catheter. Circuit resumed normal work after shutting the stopcock. The patient was weaned from ECMO successfully after 6 days without neurological dysfunction.

Case 3

A 55-year-old woman was placed on femoral venoarterial ECMO from cardiopulmonary bypass due to primary graft dysfunction after heart transplantation. During chest closure, she was hypovolemia due to massive bleeding. ECMO speed was 3,000 r/min, while ECMO flow fluctuated greatly (1.0-2.5 L/min). A small amount of air entered venous line and oxygenator. After de-airing, the pump was restarted. Meanwhile, all the venous accesses were checked safely closed. It was noticed that right atrial wall was adhered to side holes of femoral venous cannula by negative pressure. Sewing holes on atrial wall were considered as the portal of air. Another possible reason might be cavitation caused by severe hypovolemia. After volume resuscitation and sewing holes repair, no more air entered circuit. The patient was discharged from hospital 1 month later with good neurologic outcome.

Discussion

Centrifugal pump generates negative pressure in venous side of ECMO as well as venous system of patients, which will be enhanced greatly if venous limb is kinked or occlusion, or if patients are hypovolemic. Any exposure to air in venous system may introduce air into venous limb of ECMO and even into arterial side, causing air embolism. Protocol of our institute is summarized in Table 1.

Case 2 was the most familiar clinical scene of air in ECMO, and ECMO specialists were able to prevent and manage the accident quickly and successfully. Case 1 and Case 3 were special as air was introduced during complex intervention on ECMO by medical staff who were not familiar with the principle of ECMO. Because of the working property of ECMO, massive air may be pulled in by incautious procedures which is considered safe in normal conditions. Therefore, every ECMO team member should be fully aware of the risks, and perform procedures or surgeries carefully to avoid exposure to air in venous system. However, sometimes exposure to air could not be avoided. One example is catheter interventions via venous access. In our limited

experience, air intrusion could be reduced by flushing vascular catheters and retracting guidewire gently, but could hardly be eliminated. It is extremely important to monitor the circuit closely. If intracardiac shunt exists, arterial air embolism may occur, as shown in Case 1. Catheter interventions through venous access on ECMO in patients with intracardiac shunt should be regarded as high-risk procedure. We suggest ECMO should be stopped temporarily when venous access is exposed to air.

Theoretically, performing atrial septostomy on ECMO faces similar risks. However, arterial or cerebral embolism has rarely been reported.[2,3] One possible explanation is that left atrium in patient requiring atrial septostomy is of extremely high pressure, which helps prevent air bubble into left atrium. Another explanation is that risks only present near the end of the process after atrial septal defect is made. Nevertheless, in our opinion, atrial septostomy on ECMO should also be regarded as high-risk procedure.

Conclusion

Air in the ECMO circuit can never be overemphasized as it may lead to fatal consequence. Every ECMO team member should be fully aware of the risks and be more careful. Risks of air embolism increase exponentially in patients with intracardiac shunt. More attention should be paid to these patients, especially in situations when air exposure could not be avoided.

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References

1. Guglin M, Zucker MJ, Bazan VM, et al. Venoarterial ECMO for adults: JACC scientific expert panel. *J Am Coll Cardiol* 2019; 7: 698–716.
2. Lin YN, Chen YH, Wang HJ, et al. Atrial septostomy for left atrial decompression during extracorporeal membrane oxygenation by inoue balloon catheter. *Circ J* 2017; 81: 1419–1423.
3. Baruteau AE, Barnetche T, Morin L, et al. Percutaneous balloon atrial septostomy on top of venoarterial extracorporeal membrane oxygenation results in safe and effective left heart decompression. *Eur Heart J Acute Cardiovasc Care* 2018; 7: 70–79.

Case Report

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Repair of iatrogenic tracheal injury in acute respiratory failure with veno-venous extracorporeal membrane oxygenation

Pauline H Go,[1] Albert Pai,[2] Sharon B Larson[2] and Kalpaj Parekh[2]

Abstract

Iatrogenic tracheal injuries are rare but potentially serious complications of endotracheal intubation that frequently require lung isolation to repair. This is not tolerated in patients with severe respiratory failure. We describe a case in a patient with acute respiratory distress syndrome, repaired using veno-venous extracorporeal membrane oxygenation.

Keywords

Iatrogenic; tracheal injury; extracorporeal membrane oxygenation; acute respiratory distress syndrome

Introduction

Iatrogenic tracheal injuries (ITIs) are rare but potentially serious complications of endotracheal intubation, with an estimated incidence of 0.005%.[1,2] Surgical repair typically requires lung isolation. With respiratory failure, conventional airway management may not be tolerated and alternative strategies must be considered. We describe an ITI in a patient with acute respiratory distress syndrome (ARDS), successfully repaired using veno-venous extracorporeal membrane oxygenation (VV-ECMO).

Case report

A 58-year-old female (weight/height/body surface area: 55.4 kg/1.63 m/1.58 m^2) with history of depression and substance abuse presented to the emergency department with acute dyspnea and anxiety. Rapid progression to hypoxic respiratory failure and cyanosis mandated emergent intubation. Computed tomography (CT) revealed a large defect within the posterior tracheal wall with diffuse pneumomediastinum and subcutaneous emphysema of the neck and chest, severe centrilobular emphysema, and bilateral consolidation consistent with aspiration pneumonia (Figure 1). Crepitus was appreciated throughout her face, neck, chest, arms, and thighs. She was also noted to have bloody endotracheal secretions and loss of one-half the delivered tidal volume (TV). Arterial blood gas demonstrated hypoxemia, hypercapnia, and respiratory acidosis consistent with ARDS (PCO_2 51 torr, pH 7.18, PaO_2/FiO_2 148). Bronchoscopy confirmed a longitudinal laceration of the posterior tracheal wall extending from the endotracheal tube (ETT) tip to the carina.

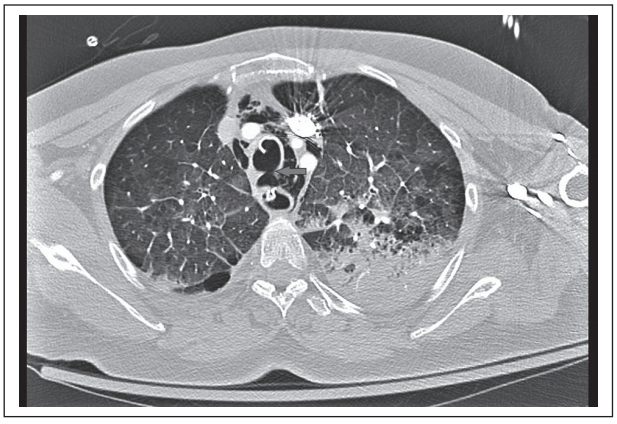

Figure 1. CT chest demonstrating large defect within the posterior tracheal wall, diffuse pneumomediastinum, severe emphysema, and pulmonary consolidation.

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Considering the length and distal extent of the injury and anticipated difficulty with lung isolation due to ARDS, the decision was made to proceed with tracheal repair using VV-ECMO. Intra-operative transesophageal echocardiogram (TEE) confirmed normal myocardial and valve function. The right internal jugular vein was cannulated with a 27 Fr. Avalon® bi-caval dual-lumen veno-venous cannula (Maquet, Rastatt, Germany) utilizing Seldinger technique. Fluoroscopy was used to guide insertion and TEE to guide positioning of the outflow lumen toward the tricuspid valve. Flow was initiated and maintained at 4-5 L per minute using a Cardiohelp system (Getinge, Sweden), with 600 mL of non-heparinized priming solution. The ETT was advanced into the left mainstem bronchus. The chest was entered in the right fourth intercostal space through a posterolateral thoracotomy. The laceration was full thickness proximally, but was partially sealed distally by the esophagus. The esophagus was dissected away from the trachea to assess the full extent of the injury. A longitudinal tear measuring 6 cm in length was identified extending to the carina but not involving the main bronchi. Primary repair was performed and the esophageal muscle wall secured over the repair to serve as a buttress. The ETT was withdrawn and secured just proximal to the repair. VV-ECMO support was maintained at full flow while employing a "resting" ventilation strategy, using TV 100 mL and positive end expiratory pressure (PEEP) 5 mm Hg. This strategy aimed to enhance lung recovery and minimize barotrauma while providing a means to maintain airway clearance and prevent atelectasis. The ETT cuff was partially deflated to reduce pressure over the repair. Systemic anticoagulation was withheld for the initial 24 hours. Continuous heparin infusion without boluses, targeting partial thromboplastin time 45-60 seconds, was initiated on postoperative day (POD) 2 once bleeding was no longer a concern. Bronchoscopy on POD 3 demonstrated intact tracheal repair with good mucosal healing. The ventilation strategy was liberalized and the patient was weaned from VV-ECMO support on POD 5 once adequate oxygenation and ventilation could be achieved with conventional mechanical ventilation, and extubated on POD 7. The patient made a full recovery without complications and was discharged in good health.

Discussion

Tracheal injury is a rare but potentially serious complication of endotracheal intubation, with potential to cause respiratory failure, sepsis, and death. The etiology isusually multifactorial, including multiple vigorous attempts at intubation by inexperienced providers, particularly in emergent settings, ETT cuff overinflation, tube repositioning with an inflated cuff or inappropriate stylet use.[3] Non-operative management can be considered in those who are hemodynamically stable, spontaneously breathing, or in whom mechanical ventilation is possible without significant volume loss, and in the absence of progressive subcutaneous emphysema, esophageal perforation or mediastinal sepsis.[1,3] In these select patients, conservative management consists of placing the ETT cuff distal to the laceration, mechanical ventilation utilizing low TV and PEEP, and early extubation.[2,3]

Surgical repair allows drainage of the mediastinum and chance of immediate cure while avoiding complications of mediastinitis and sepsis.[3] Repair of the distal trachea and mainstem bronchi is best approached through a right thoracotomy, requiring lung isolation. However, in cases of ARDS, single lung ventilation may not be tolerated and alternative strategies, such as VV-ECMO, must be considered. While the use of VV-ECMO in the repair of intra-operative tracheobronchial injury is well-described,[4–6] reports of its use in the setting of ITI and respiratory failure are limited.[7] With ARDS, the benefits of VV-ECMO also extend into the postoperative period during which extracorporeal support enables a lung protective ventilation strategy, promoting lung recovery and protecting the repair from barotrauma. Furthermore, with full VV-ECMO flow, systemic anticoagulation can be safely withheld in the immediate postoperative period until bleeding risk is reduced.

Conclusion

Our case illustrates the successful use of VV-ECMO in the surgical management of ITI in the setting of bilateral pneumonia and ARDS, and highlights the value of extracorporeal support in postoperative pulmonary and tracheobronchial recovery. The decision to proceed with VV-ECMO during surgical repair should be individualized and determined early to allow adequate resource mobilization and surgical planning prior to operation, averting the need for urgent intervention in response to unanticipated clinical deterioration.

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References

1. Minambres E, Buron J, Ballesteros MA, et al. Tracheal rupture after endotracheal intubation: a literature systematic review. *Eur J Cardiothorac Surg* 2009; 35: 1056–1062.
2. Schneider T, Storz K, Dienemann H, et al. Management of iatrogenic tracheobronchial injuries: a retrospective analysis of 29 cases. *Ann Thorac Surg* 2007; 83: 1960–1964.
3. Sippel M, Putensen C, Hirner A, et al. Tracheal rupture after endotracheal intubation: experience with management in 13 cases. *Thorac Cardiovasc Surg* 2006; 54: 51–56.
4. Fermin L, Arnold S, Nunez L, et al. Extracorporeal membrane oxygenation for repair of tracheal injury during transhiatal esophagectomy. *Ann Card Anaesth* 2017; 20: S67–S69.
5. Korvenoja P, Pitkanen O, Berg E, et al. Veno-venous extracorporeal membrane oxygenation in surgery for bronchial repair. *Ann Thorac Surg* 2008; 86: 1348–1349.
6. Antonacci F, De Tisi C, Donadoni I, et al. Veno-venous ECMO during surgical repair of tracheal perforation: a case report. *Int J Surg Case Rep* 2018; 42: 64–66.
7. Sian K, McAllister B, Brady P. The use of extracorporeal membrane oxygenation therapy in the delayed surgical repair of a tracheal injury. *Ann Thorac Surg* 2014; 97: 338–340.

Perfusion

Left ventricular venting for extracorporeal life support in phaeochromocytoma

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Giovanni Marchetto,[1] Matteo Attisani,[1] Mauro Rinaldi[1] and Marco Pocar[1,2]

To the Editor:

We read with great interest the review by Matteucci et al. regarding 62 patients with phaeochromocytoma-induced cardiogenic shock treated with veno-arterial extracorporeal life support (ECLS).[1] Reported survival was encouraging, but real-world mortality could be underestimated by the lack of unsuccessful cases in the literature. Cardiac arrest before initiation of ECLS occurred in almost 30% of the cases and was outlined by the Authors as a major risk factor for death. Intra-aortic balloon pump (IABP) counterpulsation was employed in 22% of the patients.

We successfully treated with ECLS two patients with phaeochromocytoma-induced refractory cardiogenic shock. In the former, ECLS was started during cardiopulmonary resuscitation. In the latter, cardiogenic shock was refractory despite IABP and maximal inotropic support. In both patients, additional left ventricular venting was added immediately after stabilisation with ECLS, and was obtained by direct apical cannulation and a Y-connection to the venous drainage line.[2] Recovery of myocardial function was complete in both patients, who were weaned after 5 and 6 days on ECLS, respectively. Adrenalectomy was undertaken electively, within 2 weeks.

The mechanisms of myocardial damage in this unique pathophysiological scenario are related to excessive sympathetic stimulation with increased oxygen consumption coupled with microvascular/coronary spasm and increased afterload. Elevated intracellular calcium also contributes to myocardial injury by increased oxidative stress.[3] Thus, we recommend ventricular venting to allow complete weaning from inotropes and administration of alpha- and beta-blockers to counteract the catecholamine storm and terminate the vicious cycle induced by the phaeochromocytoma.

We also believe venting to represent a key issue because IABP has not been correlated with a survival benefit, whereas left ventricular unloading reduces mortality in selected patients requiring ECLS.[4,5] More in particular, phaeochromocytoma-induced cardiogenic shock precludes the use of catecholamines for inotropic support, which are almost invariably required to optimise systolic and diastolic function, and thus coronary perfusion in patients on ECLS and IABP.

Finally, the Authors report 100% survival in the 10 patients who underwent surgical resection of the phaeochromocytoma while on ECLS. However, the reasons dictating this urgent timing are not reported. Most probably, abdominal surgery was performed in patients with ECLS circuits allowing low levels of anticoagulation. However, we advocate the complete suppression of the sympathetic storm and weaning from ECLS, favoured by ventricular venting, followed by elective resection of the phaeochromocytoma.

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References

1. Matteucci M, Kowalewski M, Fina D, et al. Extracorporeal life support for phaeochromocytoma-induced cardiogenic shock: a systematic review. *Perfusion* 2020; 35(1 Suppl.): 20–28.

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2. Centofanti P, Attisani M, La Torre M, et al. Left ventricular unloading during peripheral extracorporeal membrane oxygenation support: a bridge to life in profound cardiogenic shock. *J Extra Corpor Technol* 2017; 49: 201–205.
3. Shahim B, Faxén UL, Stern R, et al. Cardiogenic shock triggered by phaeochromocytoma crisis after an oral glucose tolerance test: a case report. *Eur Heart J Case Rep* 2019; 3: 1–7.
4. Cheng R, Hachamovitch R, Makkar R, et al. Lack of survival benefit found with use of intraaortic balloon pump in extracorporeal membrane oxygenation: a pooled experience of 1517 patients. *J Invasive Cardiol* 2015; 27: 453–458.
5. Russo JJ, Aleksova N, Pitcher I, et al. Left ventricular unloading during extracorporeal membrane oxygenation in patients with cardiogenic shock. *J Am Coll Cardiol* 2019; 73: 654–662.

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Left ventricular venting for extracorporeal life support in pheochromocytoma: Letter to the Editor – response

Matteo Matteucci[1,2] and Roberto Lorusso[1,3]

We thank Pocar and associates for their interest and comments[1] about our paper[2] on the use of ECMO in pheochromocytoma-related crisis. We would like also to congratulate them for the outstanding results obtained in their two patients, particularly for the one on cardiac arrest at the moment of ECMO implant.

We understand the position of the authors regarding the enthusiasm on LV venting and may also agree on some speculations related to the need of such an associated procedure to reduce catecholamine administration. However, two patients, although successful, do not represent a consistent and proven evidence that LV venting should be always used in these patients. Furthermore, the apical route may present several shortcomings in ECMO patients and, therefore, the choice of the type of venting might still be questionable and controversial.

We disagree with the authors regarding the benefit of IABP in ECMO patients, since a few papers did actually prove some advantages.[3,4] However, we also agree that these benefits have not been confirmed by all the studies addressing this issue, thereby leaving this topic still under debate.[5,6]

Furthermore, in patients with pheochromocytoma-crisis, ECMO is usually implanted during cardiogenic shock, as also shown in our review, with usually not negligible residual contractility, with expected unloading of the LV.

Finally, in these patients, recovery from the catecholamine-induced crisis is usually rather rapid, requiring a really short-term support.

All the above-mentioned aspects make, therefore, the actual need of a LV venting still debatable and to be verified.

In conclusion, we thank Pocar and colleagues for their additional favorable contribution in such a complex and challenging setting, underlying once more that timely and well managed ECMO support may represent a life-saving procedure which should be taken into consideration in such circumstances. Additional investigations, as in ECMO for other etiologies, are however warranted regarding the optimal configuration and application, like the need and impact of an associated LV unloading procedure.

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References

1. Marchetto G, Attisani M, Rinaldi M, et al. Left ventricular venting for extracorporeal life support in phaeochromocytoma. *Perfusion* 2021; 36: 103–104.
2. Matteucci M, Kowalewski M, Fina D, et al. Extracorporeal life support for pheochromocytoma-induced cardiogenic shock: a systematic review. *Perfusion* 2020; 35(Suppl 1): 20–28.

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3. Aso S, Matsui H, Fushimi K, et al. The effect of intraaortic balloon pumping under venoarterial extracorporeal membrane oxygenation on mortality of cardiogenic patients: an analysis using a nationwide inpatient database. *Crit Care Med* 2016; 44: 1974–1979.
4. Ma P, Zhang Z, Song T, et al. Combining ECMO with IABP for the treatment of critically Ill adult heart failure patients. *Heart Lung Circ* 2014; 23: 363–368.
5. Meani P, Gelsomino S, Natour E, et al. Modalities and effects of left ventricle unloading on extracorporeal life support: a review of the current literature. *Eur J Heart Fail* 2017; 19(Suppl 2): 84–91.
6. Kowalewski M, Malvindi PG, Zieliński K, et al. Left ventricle unloading with veno-arterial extracorporeal membrane oxygenation for cardiogenic shock. Systematic review and meta-analysis. *J Clin Med* 2020; 9: 1039.

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