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DOI: 10.1177/0267659117724865
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International survey on the perioperative management of pulmonary endarterectomy: the perfusion perspective

Roger D.P. Stanzel,[1*] Johannes Gehron,[2,3*] Matthias Wolff,[4] Natalie Striegl,[5] Peter Roth,[6] Rolf-Hasso Boedeker,[7] Christine Scheibelhut,[8] Johannes Herrmann,[9] Ingeborg Welters,[10] Eckhard Mayer[11] and Matthias Scheffler[12]

Abstract

Introduction: Pulmonary endarterectomy (PEA) is the most effective treatment available for chronic thromboembolic pulmonary hypertension (CTEPH). Patient selection, surgical technique and perioperative management have improved patient outcomes, which are traditionally linked to surgical and center experience. However, optimal perfusion care has not been well defined. The goal of the international survey was to better characterize the contemporary perfusion management of PEA and highlight similarities and controversies.

Method: The combined caseload of 15 participating centers was 5,066 cases. Topics queried included materials and types of cardiopulmonary bypass (CPB) equipment, choice of prime, fluid management, deep hypothermia strategy, temperature management, treatment of acid-base abnormalities and intraoperative hematocrit as well as anticoagulation management for heparin-induced thrombocytopenia.

Conclusion: Our assessment could provide a base for further advancement and may help design future studies to elucidate the impact of perfusion in this challenging field.

Keywords

pulmonary endarterectomy; chronic thromboembolic pulmonary hypertension; cardiovascular perfusion; deep hypothermic circulatory arrest; selective antegrade cerebral perfusion; cardiovascular surgery; centrifugal pump; roller pump; heparin-induced thrombocytopenia; circuit coating

Introduction

Despite recent advances in medical and interventional therapy, pulmonary endarterectomy (PEA) remains the most effective treatment available for chronic thromboembolic pulmonary hypertension (CTEPH).[1] A highly complex surgical intervention that has been standardized based on the protocol developed by Jamieson et al.,[2] PEA was performed on approximately 3,500 patients worldwide by 2008.[3] Proper patient selection, refined surgical technique and perioperative management have improved mortality rates from 20% to 5-10% in most centers and <5% in experienced centers.[4,5] Outcomes are linked to surgical and center experience,[6] however, it is unclear to which degree, besides providing 'high quality care', perfusion techniques and choices contribute to this. There are currently no studies providing a comprehensive examination of perfusion management. Our goal was to better characterize contemporary perfusion practice and it was hypothesized that a survey among major centers worldwide would

[1]Perfusion Services, Nova Scotia Health Authority, Halifax, Nova Scotia, Canada
[2]Cardiovascular Surgery, Dept. of Perfusion, University Hospital Giessen and Marburg, Giessen, Germany
[3]Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada
[4]Anesthesiology, Intensive Care, Pain Therapy, University Hospital Giessen and Marburg, Giessen, Germany
[5]Wetzlar Community Hospital, Wetzlar, Germany
[6]Department of Cardiovascular Surgery, University Hospital Giessen and Marburg, Giessen, Germany
[7]Institute for Medical Informatics, Justus-Liebig-University Giessen, Giessen, Germany
[8]Medical Statistics, Justus-Liebig-University Giessen, Giessen, Germany
[9]Statistics Consultancy, Giessen, Germany
[10]Institute of Ageing and Chronic Disease, Royal Liverpool University Hospital, Liverpool, UK
[11]Kerckhoff Heart and Lung Center, Bad Nauheim, Germany
[12]Department of Anesthesia, Perioperative Medicine and Pain Therapy, Dalhousie University, QEII Health Sciences Centre, Halifax, Canada

* The two authors contributed equally to the paper

Corresponding author:
Roger DP Stanzel, Perfusion Services, Nova Scotia Health Authority, 1276 Summer Street, Halifax. Nova Scotia B3L 2C2, Canada.
Email: torogerstanzel@hotmail.com

stimulate considerable interest. It is important to recognize that it was not the intention of this survey to link practices to patient outcomes. Rather, results may assist in the identification of controversies as well as help design future studies to elucidate the impact of perfusion in this challenging field.

Methods and Materials

After Institutional Review Board approval (Justus Liebig University Giessen, Giessen, Germany), a web-based survey was performed from May 2010 until June 2011, using the program *LimeSurvey*®. A total of 27 centers worldwide with an estimated surgical volume of greater than or equal to 10 per year were deemed eligible. One hundred and forty-five questions were subdivided into seven questionnaires. Contact to centers was primarily established through surgeons. Questionnaires were sent to designated members of affiliated departments of anesthesiology and intensive care and to perfusion services. No incentives were offered to participants. Eleven questions asked for information related to perfusion practice. An abbreviated follow-up survey was sent out to all respondents in May 2017 to ensure potential changes in management were captured.

Data was complemented with information from other questionnaires where appropriate. SPSS® (IBM SPSS Statistics) and Excel® (Microsoft) were used to collect and format data into figures.

Results

Data was collected on 5,066 cases. Fifteen of 27 eligible centers (55.5%) completed the perfusion questionnaire (Table 1), including three of the four largest centers worldwide. Participating centers are listed in Table 2. In-hospital mortality rates of the year 2009, as summarized for all centers, was 6.3% (median: 7.1%; range: 0% to 25%; Figure 1). Table 3 documents selected perioperative complications. Fifty-three percent of respondents used a roller pump while 47% used a centrifugal pump. The majority (93%) used open over closed circuits (n=15). Sixty percent reported using coated circuits. Of those, 66.6% used active coating (i.e., heparin-coated) while the remainder used either passive (i.e., albumin or phosphorylcholine-coated) or both types of coating. Hemolysis, hypothermia, inflammation and duration of CPB were cited as criteria influencing the choice of materials used.

The initial standard dose of heparin ranged from 300 U/kg to 500 U/kg (300 U/kg: 57%; 400 U/kg: 21%; 500 U/kg: 14%; n=13). In no case did this dose differ from regular cardiac surgical cases (n=14). A heparin dose-response curve was used by 7% (n=14). The effect of heparin during CPB was always determined by the activated clotting time (ACT) and, in 21%, managed based on heparin levels (n=14). The target ACT following protamine administration was 120 seconds (57%), 125 seconds (7%), 140 seconds (21%) or 150 seconds (14%; n=14). Residual blood (>300 ml) from the CPB circuit was routinely re-transfused by 71% (n=14).

Pulmonary endarterectomy had been performed on patients with heparin-induced thrombocytopenia (HIT) in 5 institutions (n=13). The anticoagulation strategy most commonly used was unfractionated heparin (UFH) plus tirofiban (40%), followed by UFH plus iloprost (20%), lepirudin (20%) and/or epoprostenol (20%). Of institutions where PEA had not been performed on patients with HIT, 50% indicated that they would use UFH alone while 25% would use UFH plus iloprost. Others pointed out that they would use UFH alone if HIT was remote, UFH plus nafamostat mesylate, bivalirudin, danaparoid or UFH plus epoprostenol (all: 12.5%; n=8).

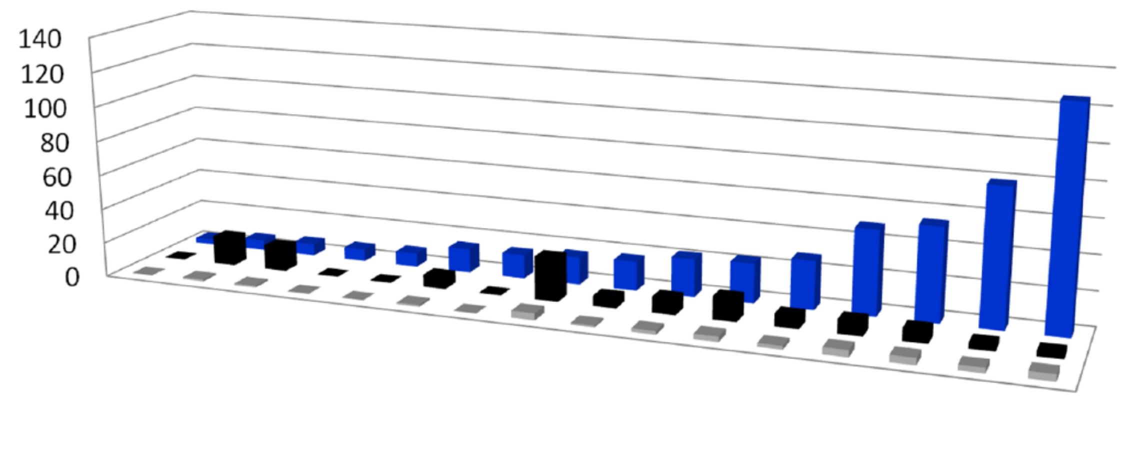
Forty-six percent of perfusionists utilized prime with crystalloid, colloid and osmotic components. However, this prime was not specific to PEA in most centers. No clear preference was given to either cerebral protection, protection of pulmonary vascular bed and cellular homeostasis as criteria influencing the choice of prime solution (Figures 2 A-C). The most common

Table 1. Details of participation in the general, anesthesia, intensive care and perfusion surveys.

Questionnaire	Response rate
General	**16 (59.2%)**
Anesthesia I/II	**14 (51.8%) / 13 (48.1%)**
Intensive Care I/II	**15 (55.5%) / 10 (37%)**
Perfusion I/II	**15 (55.5%) / 14 (51.8%)**

Table 2. Participating centers; perfusion questionnaire.

Amsterdam / Netherlands
Bad Nauheim / Germany
Baltimore / United States
Birmingham / United States
Buenos Aires / Argentina
Cambridge / United Kingdom
Chiba / Japan
Hannover / Germany
Homburg / Germany
Leuven / Belgium
Nieuwegein / Netherlands
Novosibirsk / Russia
Pavia / Italy
Prague / Czech Republic
San Diego / United States



2009 IHM (total)	0	1	1	0	0	1	0	4	1	2	3	2	4	4	3	4
2009 IHM (%)	0	16.6	14.3	0	0	7.1	0	25	5.9	9.1	13	7.1	8.2	7.4	3.8	3.2
n (2009)	3	6	7	7	8	14	14	16	17	22	23	28	49	54	79	126

Figure 1. In-hospital mortality (IHM) rates of 16 centers, related to center volumes, as obtained from the general questionnaire completed by surgeons. Thirteen of 16 centers shown are reflected in the perfusion part of the survey. In-hospital mortality rates of the year 2009 as summarized for all centers were 6.3%. The median of center mortality rates was 7.1% (range, 0% to 25%).

Table 3. Prevalence of perioperative complications following pulmonary endarterectomy. Results were obtained from ICU questionnaire completed by intensivists.

Type of complication (ICU questionnaire)	Overall prevalence and average	Ranges among centers	Indications based on data from n=centers
Major neurological complications (stroke, persisting neurological deficit)	7/269 2.6%	0–12.5%	n=10
ARDS	3/269 1.1%	0–7.1%	n=9
Severe reperfusion pulmonary edema	12/269 4.5%	0–42.8%	n=9
Severe hemorrhage requiring rethoracotomy	10/272 3.7%	0–10.1%*	n=10
Re-thrombosis of pulmonary artery	1/269 0.4%	0–4.5%	n=10

*8 of 10 occurred in a single center. ARDS: adult respiratory distress syndrome.

temperature reference sites were the bladder (27%) and nasopharyngeal (20%). Tables 4A and 4B describe cooling and rewarming gradients. Sixty-seven percent used vasodilating agents during patient cooling and rewarming (Figure 3). All respondents used deep hypothermia (range, 16-24°C, median, 18°C). Deep hypothermic circulatory arrest (DHCA) was employed by 87%, while selective antegrade cerebral perfusion (SACP) was reported by 13%. Sixty-three percent indicated that adequacy of DHCA should be evaluated. Factors considered to be appropriate measures of DHCA included temperature, near-infrared spectroscopy (NIRS), bispectral index (BIS), electroencephalography (EEG), venous saturation and acidosis. Fifty-four percent recorded the lowest venous saturation during re-establishing flow after DHCA. Figures 4A and 4B document the defined duration and variation in actual duration of DHCA.

Sixty-four percent indicated that the treatment of acid-base abnormalities was important during hypothermia. The most common approach was alpha-stat only (56%) while 11% used pH-stat only and 33% used a combination; the most common criteria affecting management were cerebral protection (86.7%) and cerebral perfusion (66.7%; Figure 5). All respondents indicated that intra-operative hematocrit (Hct) was

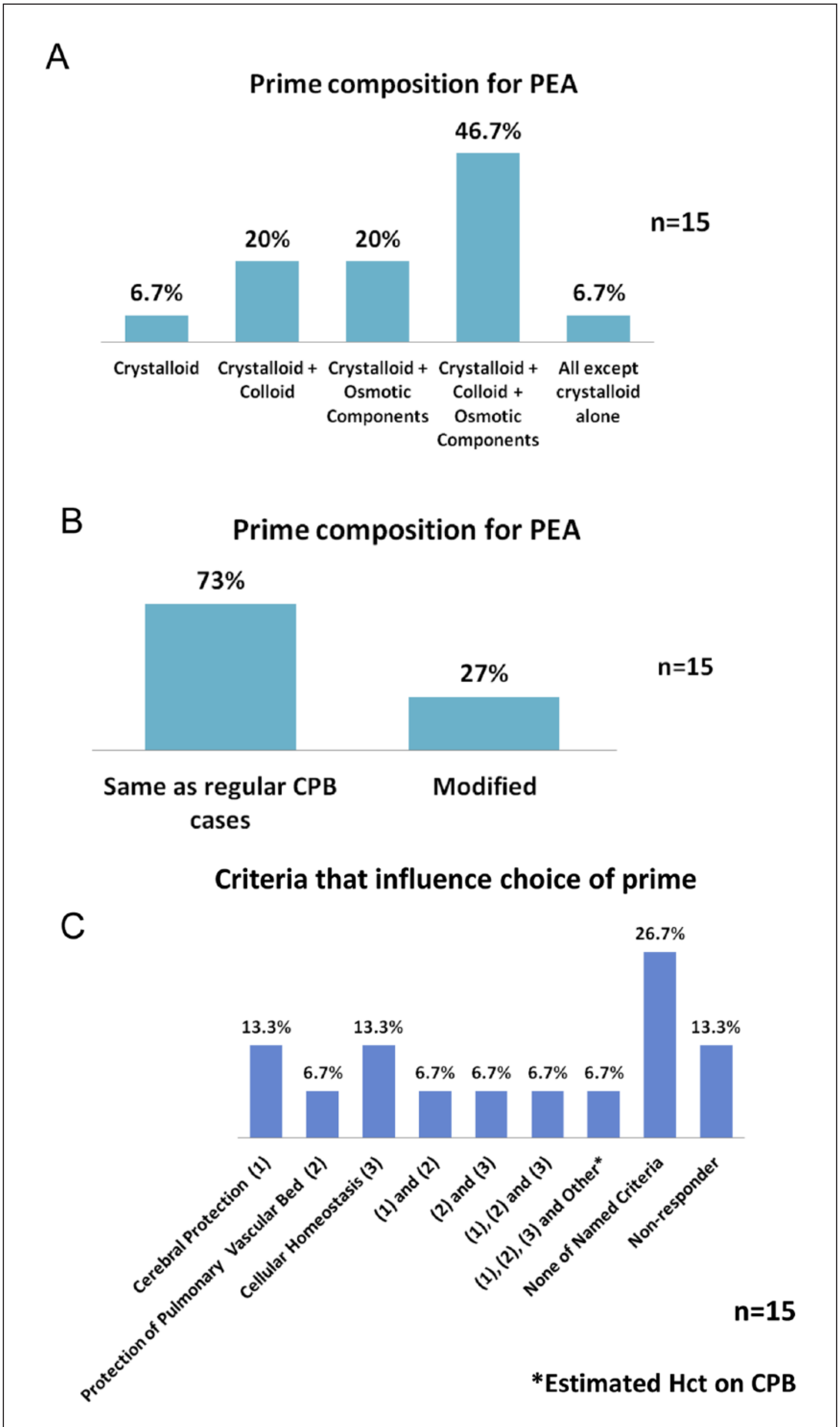


Figure 2. Fluid management and choice of priming fluid. Prime choices (A) and their specificity for PEA (B). Criteria influencing the choice of fluid used (C). Multiple responses were acceptable.

Table 4. Temperature reference sites and gradients. Details of patient cooling (A) and of patient re-warming gradient strategies as provided by participants (B).

A

Gradient (°C)	Gradient Details
5	Water-to-venous blood
<5	Bladder-to-nasopharyngeal. Also, <10 arterial blood-to-bladder
10	Bladder-to-water
10–14	None provided
15	None provided
10	Arterial blood-to-bladder
10	None provided
4	None provided
6–10	Perfusate-to-patient
5	Arterial inlet-to-bladder
5	None provided
15	Water-to-rectal

B

Gradient (°C)	Gradient Details
5	Water-to-venous blood
<5	Bladder-to-nasopharyngeal. Also, <10 arterial blood-to-bladder
10	Bladder-to-water
8–10	None provided
8	None provided
10	Arterial blood-to-bladder
10	None provided
4	None provided
6–10	Perfusate-to-patient
3	1_0C/minute
2–4	Nasopharyngeal-to-bladder
8–10	Water-to-rectal
5	Bladder-to-arterial blood
10	Water-to-rectal

important. Table 5 lists underlying reasons. Figures 6A and 6B document target Hct during and prior to weaning from CPB.

Significant hemodynamic compromise caused by right heart failure was primarily treated by drugs. Mechanical support, such as right ventricular assist device (RVAD, 21%), intra-aortic balloon pump (IABP, 21%) and extracorporeal membrane oxygenation (ECMO, 14%) played a minor role (n=14).

Updated information from the year 2017 was obtained from nine centers. Recent practice styles from 2017 were compared to earlier practices captured in the initial survey. Areas with no change included arterial pump type, open versus closed circuit, use of DHCA or SACP and definition of periods of circulatory arrest. However, changes occurred in other fields. Five of nine centers changed coatings, whereby one center stopped using coating and four, which initially had no coating, reported using coating now, reflecting a trend towards coating. There was no consensus regarding the type of circuit coating. Despite the increased use of coatings, no inference can be made about its benefit.

The initial trend for prime composition was the use of crystalloid with colloid and osmotic agents (46.7% of centers). In the follow-up survey, four of nine centers reported using the same prime, with a trend from the remaining five centers towards colloid usage, either using colloids in place of osmotic agents or adding colloids to the previous prime. All responding centers reported an increase in the number of temperature reference sites. While three of nine centers remained unchanged in terms of cooling/re-warming gradients and one reported a decrease by 5°C, the overall trend was an increase in gradients (5 of 9 centers, range: 2-7°C; most common increase: 5°C). Five of nine centers used the same vasodilating agents during cooling/re-warming. Of the four centers that changed their practice, two now use vasodilating agents, while two do not. Three of nine centers maintained the same acid-base strategy. Of the remaining six centers, three initially declared that an acid-base strategy was not important, but have since used a specific approach. The consensus strategy was pH-stat for cooling and alpha-stat for re-warming. Three of seven centers reported the same intraoperative target hematocrit while the remaining four centers reported increased target values.

Discussion

While expert perfusion care is mandatory for achieving favorable outcomes in PEA,[9] the significance of specific strategies can only be defined from a thorough assessment of practices used. To this end, this international survey describes practice styles and trends of contemporary perfusion management for PEA. Its response rate ranged within those of other surveys conducted among perfusionists.[7,8]

The survey identified a near equal frequency in roller and centrifugal pump usage. Given the convention that centrifugal pumps may be less damaging than roller pumps,[10] this was unexpected, but issues such as cost, lack of familiarity and hardware may contribute to this. While a recent prospective randomized study investigating the impact of main pump heads could not demonstrate any differences in clinical outcomes, the observed reduction in inflammatory mediators 24 hours after surgery and the potential for improved patient outcomes has not gone unrecognized.[11,12] With regard to evidence of reduced coagulation, complement activation and enhanced platelet preservation,[13,14] the fact that

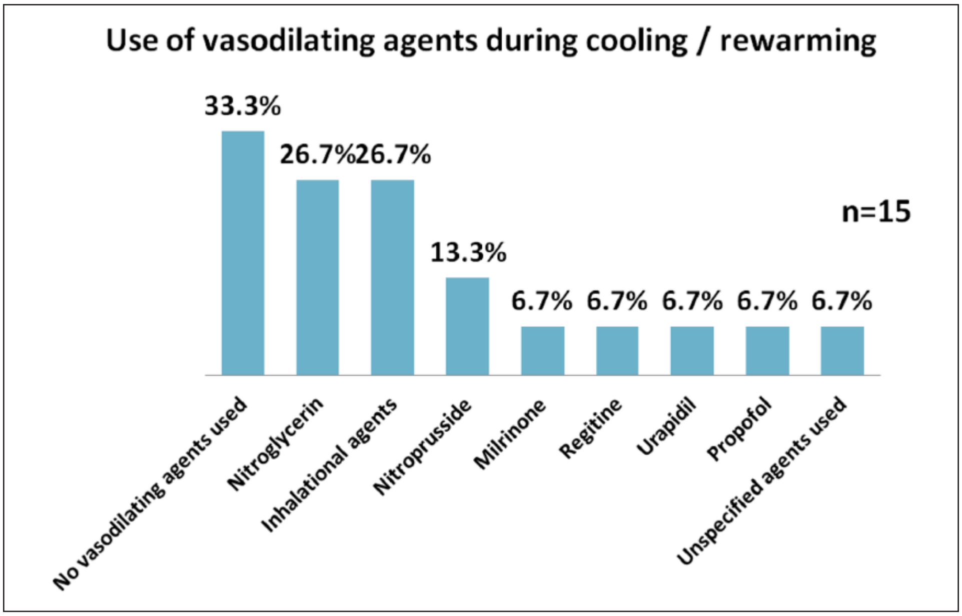


Figure 3. Details of vasodilating agents during cooling/re-warming. Multiple indications were acceptable.

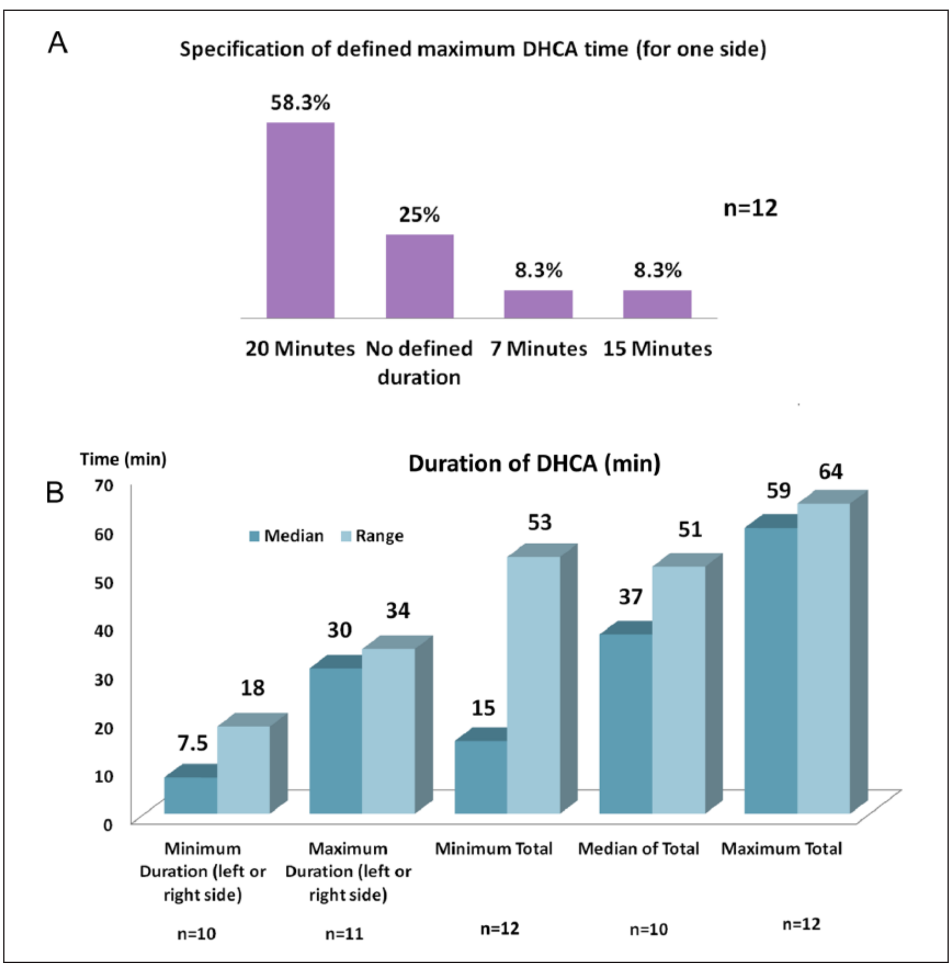


Figure 4. Duration of circulatory arrest. Maximum defined period of deep hypothermic circulatory arrest (DHCA) to either left or right side of the centers that have a defined duration of DHCA (n=12) (A). Data pertaining to duration of circulatory arrest reported of the year 2009: minimum (left or right side), maximum (left or right side), minimum total, median of total and maximum total (B). Data are median and range of data from all respondents.

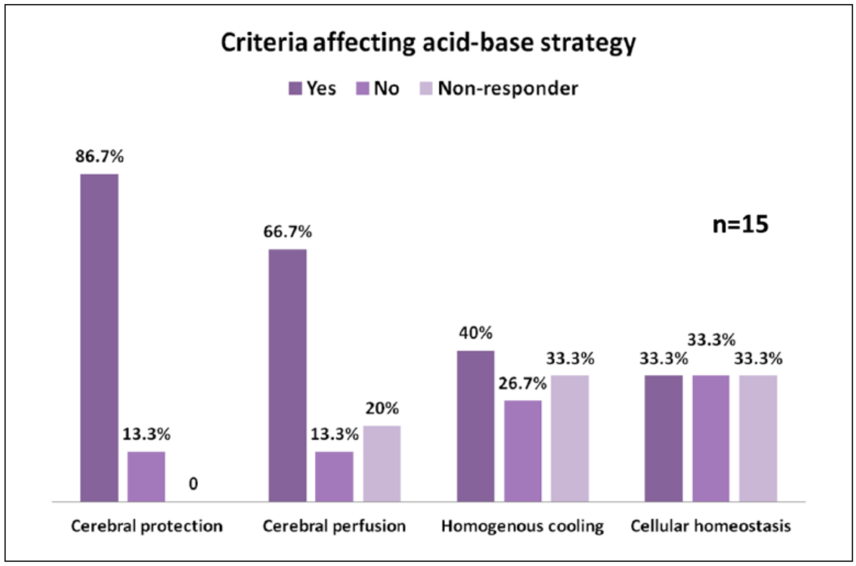


Figure 5. The most common criteria affecting acid-base strategy. Multiple responses were acceptable.

Table 5. Reasons why intraoperative Hct were reported to be important (n = 14).

Circulatory arrest and rheology
Accept lower Hct with hypothermia, usually hemodilute and take off 1-3 units of blood going on to CPB
Blood viscosity
Maximizing oxygen delivery
To have a good oxygen delivery
Hct of 28 and modified pH-stat blood gas management. Similar to Boston Children's circulatory arrest studies
The majority of these patients are polycythemic. To improve microcirculation during cooling, we "bag" 1-2 liters of blood and give additional crystalloid and colloid solutions to reduce the Hct. During re-warming, as oxygen uptake is increased, blood is returned to the patient, with excess fluid hemoconcentrated
High Hct will result in perfusion problems in the capillaries. Low of Hct will result in insufficient organ oxygenation
Like Hct not to be less than 25% before circulatory arrest and above 28% at termination of bypass
Because of hypothermia, we dilute the blood for better viscosity (Hct about 25%).
During DHCA, Hct <20%
Capillary density, oxygen transport

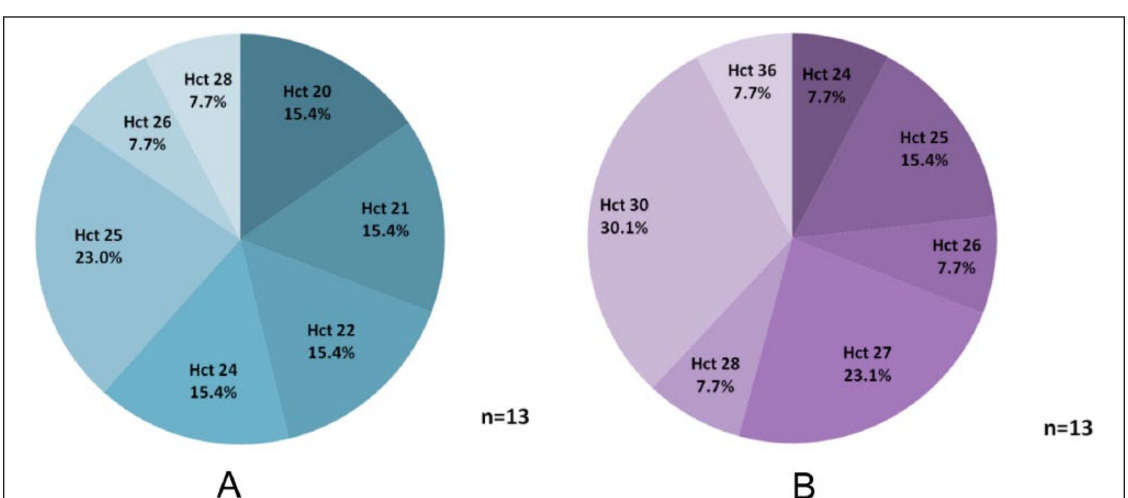


Figure 6. Target Hct during (A) and prior to weaning from CPB (B).

numerous centers used uncoated circuits was also unexpected, but may be a cost-related decision. While there was considerable variation in composition, the prime was the same for PEA as for regular practice in the majority of centers. Unfractionated heparin plus the glycoprotein IIb/IIIa inhibitor tirofiban, as detailed by Banks,[15] was used by centers with experience in managing cases with HIT. It is unknown whether these cases were still testing positive for HIT antibodies as, in elective cases, one would usually prefer using unfractionated heparin alone.[16] Recombinant hirudin was not used, presumably because of the increased bleeding risk[17,18] and neither was bivalirudin which is favored in the case of surgical urgency, likely based on the elective nature of PEA.[16]

Few centers employed selective antegrade cerebral flow (SACP), which has generally been demonstrated to improve neurological outcomes.[19,20] In contrast, DHCA alone has been considered safe for periods up to 25 or even 50 minutes.[21,22] The prospective international PEA registry also demonstrated favorable outcomes with DHCA alone. However, its duration was a significant risk factor for developing neurologic complications,[6] a consideration that was also reflected in survey data reported. Several studies failed to improve outcomes with SACP over DHCA.[23-25] Whether these results can be applied to smaller centers where longer or more frequent DHCA times may prevail remains unclear and the optimal strategy for neurological protection in PEA is, perhaps, not completely understood. A narrow majority felt that the adequacy of DHCA should be addressed, an unexpected response given the importance of reducing cerebral metabolic demands during DHCA. Hct targets during CPB and before weaning were relatively high; however, there is no evidence as to why patients undergoing PEA would require higher hematocrit levels than a standard cardiac surgical population. The operation has originally been described as requiring transfusion only in a few patients, a finding that was recently confirmed.[2,26] ECMO, viewed as a standard of care measure for severe post-endarterectomy complications,[27] was infrequently used, similar to the European/Canadian CTEPH Registry.[6]

Updated information from the year 2017 suggested that pump and circuit type used, as well as general circulatory arrest strategy and arrest times, largely remained the same. There was a trend towards using circuit coatings, which is fitting given the evidence for the utility of coatings.[28] There was also a trend towards an increased use of colloids, either in addition to the original prime or in place of osmotic agents. The updated information demonstrated a tendency towards using greater temperature gradients during cooling and re-warming. Acid-base management strategy was no longer considered as being of low importance by almost half of the centers which were available for follow-up. A slight trend towards higher Hct targets was observed in 2017 compared to 2010/2011, potentially a result of recent evidence suggesting that a restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity or healthcare costs.[29]

Survey data have identified a number of similarities and differences. Various publications in cardiac surgery, anesthesia and intensive care medicine describe how care provided to patients undergoing PEA may differ markedly from standard care.[2,5,9,15] Accordingly, there is a role for research in perfusion to identify if, where and why changes to conventional techniques should be made.

An important limitation of this survey is that the data presented are aggregate data from 15 out of 27 centers and, thus, may not be representative of the whole sample. While it is tempting to link individual practices with outcomes, this was beyond the goal of the survey and results would have to be interpreted with caution. The survey did not provide data on myocardial protection as it was felt that this belonged more to the realm of surgery, which is otherwise highly standardized and has been described elsewhere.[30]

Summary

Exceptional perfusion practice remains an integral part of perioperative care for PEA. However, the impact of single techniques has not been well defined. This survey identified several fields with considerable variance, i.e., roller pump versus centrifugal pump, coated vs. uncoated circuits and prime choices. Vasodilators were frequently used during patient cooling and rewarming. The use of DHCA prevailed while SACP was infrequently employed. Almost half of the institutions had experience with managing HIT, preferably using UFH plus tirofiban. Intraoperative Hct was considered important with median target hematocrits for weaning from CPB of 27%.

Updated information from the year 2017 suggests that pump and circuit type, as well as circulatory arrest strategy, largely remained unchanged. There was a trend towards using coated circuits, increased use of colloids and higher temperature gradients during cooling and re-warming. Acid-base management was generally considered of greater importance, with a consensus of pH-stat for cooling and alpha-stat for re-warming. A slight trend towards higher Hct targets was also noted.

The variance observed raises the question whether there is future potential for standardization, either in the way of practice recommendations or of guidelines. Ideally, randomized, controlled, multicenter trials linking specific perfusion strategies to patient outcomes should be performed among centers with similar perioperative management such that optimum care can be defined in this challenging field.

Declaration of Conflicting Interests

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

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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