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Human Factors and the Cardiac Surgical Team: A Role for Simulation

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Abstract: Human factors play an important role in determining the outcome of cardiac surgery. The interaction of humans with their equipment, and with each other in teams, is critical to success. Simulation provides a means of teaching and assessing the technical and non-technical skills of clinicians and can facilitate research into interventions to improve safety. Simulation in anesthesia has taken much from aviation and provides a model that could be extended to perfusion. The cost of setting up a simulation center (or even of adding a perfusion simulator to an existing center) is relatively high, but the potential return on this investment is also substantial, particularly at a time when access to patients for teaching and research is becoming harder. Different degrees of complexity and fidelity in simulation lend themselves to different objectives, whether in teaching, assessment, or research. In the longer term, comprehensive simulations of cardiac surgical procedures involving all participants in meaningful simulated roles may be possible. **Keywords:** human factors, simulation, cardiac surgery, performance. *JECT. 2007;39:264–266*

INTRODUCTION

The contribution of human factors to outcome in cardiac surgery has become increasingly obvious over the last few decades (1–5). Human factors is a domain shared by professionals from almost any health care background who become interested, not as much in advancing the science of their subject, as in the safe and effective application of that science to patient care. A large part of this involves improving aspects of teamwork. Cardiac surgery is a field of surgery in which teamwork is particularly important. Close communication and coordinated activity between the perfusionist, the anesthetist, the nursing staff, and the surgeons (primary and assistant) is essential.

In one traditional view, human factors involves observation in the field, identification of ergonomic deficiencies in equipment or the wider system, addressing these through innovations intended to facilitate the interaction between humans and their environment (with an emphasis on technology), and evaluating these innovations using various clinical research methodologies. It is primarily about improving the design of the things humans use in their work or in their everyday life (6,7). In health care, there has been a strong move to shift the emphasis when things go wrong to addressing the system rather than the people who work within it (8). However, the easy gains in safe system design have mostly been made, and the greatest opportunity for future improvements in the performance of the cardiac surgical team lies in recognizing that the human is a key element of the complex system of health care (9,10). The human may be the hardest part of any system to change (11), but it is a part that cannot be ignored. It is a matter of improving all elements of the system together. The aim should be to make it easier for clinicians to do their job, but at the same time also to include training and the promotion of attitudinal change to improve human performance and ensure that advantage is taken of innovations in equipment, drugs, or the environment. In health care at least, most initiatives to improve safety depend on some degree of engagement by the people who will interact with them. This implies education. It implies evaluation of clinicians (12) and of equipment and of the interaction between the two (13,14). It also implies research into the performance of clinicians, particularly in teams (15), and particularly in relation to non-technical skills (16), notably when stressed or fatigued (17). In each of these activities, simulation provides a novel and potentially very powerful tool with many potential advantages over the clinical environment (18–20).

Simulation for all of these purposes is used in a number of industries, is very well established in aviation, and is gaining traction in health care generally and in anesthesia

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in particular. Simulation has been used in perfusion (21) (R. Morris, personal communication, 2007), and simulators of varying sophistication are now available for a range of surgical procedures (22).

Anesthesia provides a good case study for the application of simulation to perfusion. Simulation centers of anesthesia are proliferating, but there are few standards, and there is considerable variation in infrastructure and expertise. Commercially available anesthesia simulators have many powerful attributes, but also limitations, notably in physiologic and pharmacologic modeling and in reliability. Skeptics criticize high costs, limitations in realism, and lack of validation and remind us that findings or experiences in the simulator may not apply to the clinical situation (23–25). It has been estimated that setting up a simulation center in the United States cost approximately US$876,000 and running it costs approximately US$361,000 per year (26). In health care, the competition for limited resources for training and research is intense. Many simulation centers have found financial sustainability elusive. An optimistic rush to adopt simulation from aviation has given way to increased recognition of the hard realities of actually using it effectively to improve outcomes for our patients.

It is possible to categorize simulators in several different ways (20). The fidelity of the simulation experience is as much about the simulated environment and the contribution of role-playing participants as the simulator. Nevertheless, a key aspect of simulation for clinical fields such as anesthesia and perfusion is the modeling of physiology. The degree to which this is realistic and autonomous is critical for high-end simulation training, evaluation, and research. At present, there is much still to be done before the modeling of physiology and pharmacology in anesthesia simulators permits the type of training and evaluation currently accepted as the norm in aviation.

Simulation has several attributes of value to adult education, relevant to the cardiac surgical situation (19). It allows learners to be actively engaged in the educational process, in solving real life problems, and in gaining relevant (albeit simulated) clinical experience, and it provides opportunities for practice, for feedback, and for reflection (27). Simulation has been used to impart knowledge and teach skills in many medical disciplines. However, evidence that simulation enhances education is limited: outcome measures have varied, and controls have been few and not always the most effective alternative educational methods available. The assumption that simulation provides the answer to modern day barriers to learning on patients is far from proven. Effective learning is dependent on educational principles that apply whether simulation is used or not, and these are sometimes neglected by enthusiasts for simulation. Clarity about the objectives of any educational exercise is essential. The choice of educational method should be informed by the nature of the task in question, not by the fact that one happens to own a simulator. The use of shortcuts to facilitate simulation-based education may actually serve as a poor role model for clinical practice and have the unexpected and undesirable effect of teaching bad habits. The notion that simulation is worthwhile in itself is as much a trap for the tyro educationalist as opposition to simulation may be an impediment to progress for some traditionalists.

The gold standard for research into clinical questions is to study them in real patients, but barriers to doing this may include risk to patients, the fear of medico-legal repercussions for participants, and the cost when the events of interest are rare and large studies are needed. With simulation, clinical scenarios can be standardized, participants can be observed and videotaped, rare events can be produced on demand, and the environment is relatively safe for all concerned (15,28). Our New Zealand group is developing and refining a model for research into human factors in the operating room. We are using a multilayered approach, which involves studying the same question at different levels of simulation, beginning with simple and efficient micro-simulations and validating findings in more comprehensive and realistic scenarios. We are collaborating with the Institute of Biomedical Engineering at the University of Auckland to improve the autonomous physiologic and pharmacologic models of our simulator to enhance our capacity to use powerful, objective, task relevant outcome measures in our research, such as severity and duration of hypoxia or hypotension. The next step will be to integrate simulators relevant to surgery and perfusion and increase the proportion of participants in our scenarios who are subjects of the research, functioning as a team, rather than faculty playing roles.

Simulation-based assessment is accepted in aviation, and pilots who fail are immediately stopped from flying until remedial training can be provided and competence shown at a repeat assessment. Because it is thought that evidence for the validity of simulation for the assessment of anesthetists is still needed, there has been reluctance to use simulation in the assessment of anesthetists, at least in New Zealand and some Australian units. It is time to reevaluate this position, even if conclusions about competence are restricted to the context of the simulated environment. Our experience in research suggests that many participants appreciate explicit feedback and would gain from knowing whether they have achieved acceptable levels of performance or not. There is no greater reason to doubt the relevance to clinical practice of performance in a simulator than there is to doubt that of performance in a multiple-choice examination, and the use of simulation for this purpose is probably overdue.

A project to provide simulations genuinely relevant to

perfusionists and cardiac anesthetists in the Auckland center is probably the next step, with the addition of meaningful simulated surgical tasks to integrate surgeons into the simulations as a longer-term goal. This will require funding for the purchase of a perfusion simulator, or alternatively (given very limited availability), the development of such a simulator locally.

Having obtained or developed the perfusion simulator, our experience suggests that considerable work will be needed to achieve convincing simulations of relevant scenarios. It is logical to begin with training. The ideal would be to develop modules to teach psychomotor or cognitive skills (such as advanced ECG recognition, technical tasks for perfusionists, and advanced interpretation of blood gas and coagulation test results for all participants), which can be integrated into complex scenarios focused on the use of these skills within the team, under pressure, while caring for the simulated patient. From experience in anesthesia, it is likely that such a course would be relevant to both trainees and advanced practitioners. Once a credible course has been established, consideration can be given to extending the objectives to evaluation of the performance of participants. More excitingly, it will be possible to adapt the scenarios for use in human factors research directly related to perfusion, cardiac anesthesia, and, in time, the whole cardiac surgical team.

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Cannulae and Cell Saver Design: Do They Make a Difference?

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Abstract: In the evolution of cardiopulmonary bypass (CPB), it is becoming increasing obvious that minimizing microembolization is critical in protecting the brain. Every component of the CPB circuit and ancillary apparatus must be evaluated and, if necessary, re-engineered with the reduction of microemboli a major focus. Cardiotomy suction has been identified as a major source of lipid microemboli. However, is the alternative blood treatment apparatus, the cell saver, capable of reducing the lipid embolic load and are all cell savers equally efficient? In the event that microemboli do make it to the aorta, is it possible to divert them away from the brain to more robust vascular beds through clever design of the aortic cannula? Is the venous cannula a source of microgaseous emboli? The answer is yes to both questions. Emboli can be directed away from the brain by the positioning and design of the aortic cannula and the venous cannulae may be a source of gaseous microemboli delivered to the oxygenator by the venous line but careful practice will prevent this type of embolic formation. **Keywords:** brain injury, microemboli, cardiopulmonary bypass. *JECT. 2007;39:267–270*

INTRODUCTION

Embolization is a major cause of morbidity secondary to cardiopulmonary bypass (CPB) and cardiac surgery procedures. Careful monitoring reveals when embolization occurs (1–4) and suggests methods to reduce the number of emboli that reach the brain (Figure 1), such as changing clamping procedures (5,6), using improved cannula, and changing cardiotomy suction (7) and cell saver (8,9) protocols.

The return of contaminated shed blood from the thoracic cavity during CPB, through the cardiotomy reservoir, is associated with lipid (LME) and gaseous (GME) microembolization. The passage of deformable GME or LME, through the vessels of the brain, results in a break down of the blood–brain barrier with associated brain swelling (10). Furthermore, the level of inflammatory mediators and the systemic inflammatory response (SIR) is increased through contact activation caused by the blood being damaged by suction and prolonged contact with non-biocompatible surfaces (11,12). Transfused blood products also contribute to SIR, partly because the route of administration is through the cardiotomy reservoir where the fresh blood products are mixed with contaminated suctioned blood.

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AVOID THE RETURN OF CARDIOTOMY SUCTION BLOOD

Defining the term shed blood has been difficult. However, it is well documented that blood in the thoracic cavity is contaminated with lipid material from the cut surfaces of the sternum (7). Suctioning causes gaseous microemboli to be coated with lipid and protein material and become particulate emboli with a gaseous core. The passage of these emboli through the micro-vasculature contribute to the breakdown of the blood–brain barrier and potentially the systemic inflammatory response syndrome.

IS THE CELL SAVER THE ANSWER

Patients who stay in the intensive care unit for >2 days receive a third more cell saver blood than patients discharged in <48 hours (Table 1). Is it the shed blood or the increased blood loss that causes the more problematic outcome? The studies of Aldea et al. (13), as well as Dr. Hammon's data (personal communication; Table 1), supports the contention that minimizing blood loss results in better outcomes.

It seems that treating shed blood through the cell saver may not be the panacea expected. Kincaid et al. (8) performed a series of experiments in a canine model of CPB to determine whether different cell savers and filters handled lipid emboli equally well as shown in the cerebral

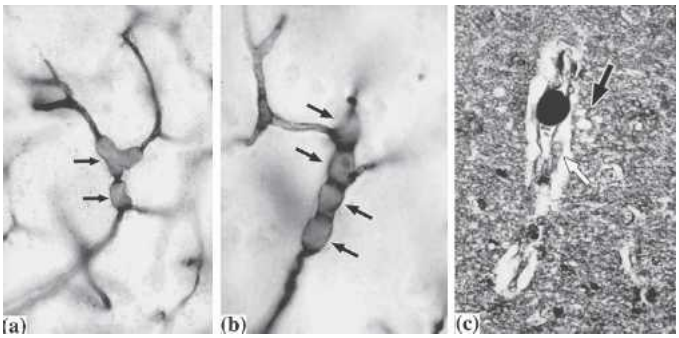

Figure 1. Lipid microemboli from human autopsy after CPB. High-magnification photomicrograph of microlipid emboli from patients who died after CPB. Original magnification, ×50. A and B, Microemboli at bifurcation points (arrows) in 100-mm-thick celloidin sections with AP microvascular staining. C, A microembolus stained black with osmium indicates that it is lipid. Swollen astrocytic end-feet (white arrow) and vacuolization in the adjacent neurophil (black arrow) indicate tissue injury. This is a paraffin-embedded, 5-mm-thick osmium-fixed section (courtesy Professors D. Moody and D. Stump, Wake Forest University School of Medicine, Winston-Salem, NC).

Table 1. Cell saver volume and the length of intensive care unit stay.

ICU Stay	*n*	Cell Saver Amount (Mean ± SD)
<24	43	631 ± 234
24–48	55	680 ± 256
>48	40	829 ± 344

*$p < .05$.
ICU, intensive care unit.
(With permission Professor John Hammon, MD, Cardiothoracic Surgery, Wake Forest University School of Medicine, Winston Salem, NC).

vasculature by small arteriolar dilatations (SCADs). The wide variability in cell saver performance is shown in Figure 2.

THE SOLUTION

Most important is a consensus definition of what is shed blood and/or waste blood and how to quantify the volume of blood either returned or processed. Actual quantification often leads to improved blood management.

Reducing the quantity of shed blood that must be processed and returned to the patient through the cardiotomy reservoir or cell saver is a first priority. Improving the quality of the returned blood through better filtration and blood management is also critical. This can be accomplished by instituting several measures to either reduce bleeding or the volume of blood displaced from the patient:

1. Aggressive surgical techniques to minimize bleeding as it occurs.
2. Aprotinin should be used, when appropriate, to reduce blood loss and protect the patient from inflammatory processes.

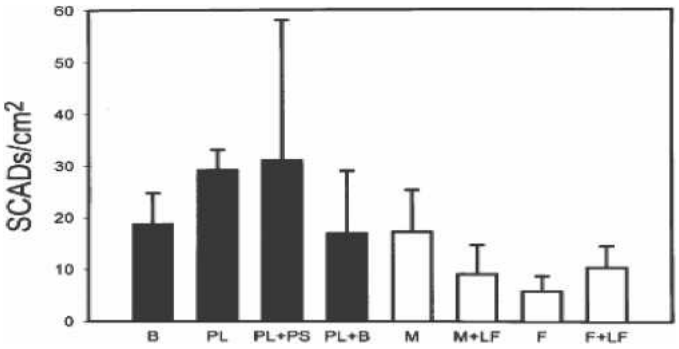

Figure 2. Mean small capillary and arteriolar dilation (SCAD) density ± SE by filter or processed salvaged blood (cell saver) group. Closed bars represent arterial filter group; open bars represent cell saver group. $p < .05$ for cell saver vs. arterial filter groups; $p > .05$ for all other intergroup comparisons. (B, Bentley Duraflow II AF-1025D; PL, Pall Leukoguard AL; PS, Pall Stat Prime; M, Medtronic Autolog Cell Saver; LF, Pall RCXL 1 leukocyte removal filter; F, Fresenius Continuous Autotransfusion System) (from Kincaid EH, Jones TJ, Stump DA, et al. Processing scavenged blood with a cell saver reduces cerebral lipid microembolization. Ann Thorac Surg. 2000;70:1296–300, with permission).

3. Possibly, microcircuits (or minimizing the current system) should be used to minimize blood dilution and the need to return cardiotomy suction shed blood.
4. The arterial filter should not be purged to the cardiotomy reservoir.
5. A 20-μm gravity filter placed between the cardiotomy reservoir and the CPB circuit greatly reduces the number of gaseous microemboli.
6. A 20-μm arterial line filter is superior in reducing the number of detectable microemboli coming from the CPB circuit.

Suctioned blood from the thoracic cavity is contaminated with lipid and gaseous microemboli and surgical debris. The contents are dilute with saline and cardioplegia solution, as well as being rich in inflammatory mediators and low in red blood cells. Shunting a fairly large volume of clean blood from the arterial filter and mixing it with the contaminated cardiotomy suction blood almost insures that the contents of the cardiotomy reservoir will have to be returned to the patient. The lipid and gaseous contents of the reservoir also degrade the performance of the arterial filter. Our perfusionists use a venous bag and return blood products through a closed system.

CAN CANNULA DIVERT EMBOLI FROM THE CIRCUIT AWAY FROM THE HEAD VESSELS?

We have performed extensive tests for industry to determine whether changes in aortic cannula can reduce the number of emboli detected in the left carotid artery during simulated CPB and during human coronary artery bypass grafting (CABG) procedures, as well as canine models. We participated in the development of the Cardeon Cobra cannula, which segmented the aortic arch with a physical

barrier that did reduce embolization, as well as provided differential cooling for the head and the body (14). In addition, we have performed extensive testing for the Edwards Embol-X System, which deploys a filter in the aorta to trap emboli during clamping (15). The laboratory has been extensively involved with Medtronic (Medtronic, Minneapolis, MN) in the development of the 3-D cannula that uses an innovative porting system to carry emboli away from the head vessels. The simulated methodology is as follows.

STUDY GOALS

Compare and contrast various cannula designs on the behavior of aortic GMEs.

- Document the behavior of GMEs exiting the cannula into the aortic arch via videotape; i.e., spiraling of GME, aggregation of GME, formation of macro-air bubbles, etc.
- Measure the transit time of GMEs and macroemboli through the aortic arch through videotape.
- Count the number of GMEs that transit the left carotid using the EDAC embolus detection system.

METHODS

A water-glycerol solution [42% glycerol (Sigma Aldrich G7757] with water solution (~30 L) was prepared in a black plastic tub (17 in. width × 30 in. length × 14 in. depth) with a viscosity similar to blood and was circulated through a model aorta, closely resembling the human arterial system. The aorta model was configured using 3/8" tubing with a ½″ tubing segment through the roller head pump (700 MDX, Sarns, Ann Arbor, MI). Hoffman clamps were used to regulate the outflow and pressure of the aortic model to regional physiologic levels associated with CPB. The completed circuit was warmed (36.5–38.3°C) as it was constantly circulated through a Biotherm Heat Exchanger (61399400964; Medtronic) connected to a Sarns Cooler/Heater (11160; Sarns, Ann Arbor, MI). Aortic pressure was monitored from the left iliac artery site. The proximal aortic arch was videotaped during each trial to visualize the distribution of GMEs of each cannula within the arch to the major vessels directed towards cerebral blood flow.

Air (5 mL) was introduced after the roller-pump and 50 cm before the cannula as a rapid bolus or as constant streaming air (30 seconds @ 0.16 mL/s) at flow rates of 4 and 6 L/min. The streaming air was delivered using a Harvard syringe pump connected to the circuit through 60″ small bore tubing (priming volume = 1.7 mL). Streaming air was delayed reaching the circuit because it was necessary for the compressing air to overcome the perfusion pressure of the circuit. The syringe pump was turned off 30 seconds after streaming air began to enter the arch.

GMEs were counted using an embolus detection and classification (EDAC) (16) transducer positioned onto the left carotid ~25 cm distal from the aortic arch (Figure 3).

EDAC data were collected for a 2-minute period either beginning 1 second before each 5-mL air bolus injection or beginning 1 second after the appearance of streaming GMEs within the aortic arch.

We tested 14 different cannula, not all of which are commercially available, and the results were quite revealing. It is absolutely possible to minimize brain embolization with clever cannula design. Any porting is superior to just a straight J, but porting must be done with view toward more than just changing the pressure gradient. There was a >2-fold decrease in the number of emboli detected in the left carotid with the best performing cannula. However, some cannula accomplished this by diverting most of the emboli up the right carotid. Others shredded large bubbles in to many small ones, resulting in higher counts of clinically less significant GMEs. Lipid microemboli handling characteristics are not the same as GME handling attributes. Therefore, we await the outcomes of the clinical trials.

While monitoring emboli counts from the arterial filter, we also documented emboli returning from the venous line. The question was had these emboli completely passed through our canine model? We determined that when the siphon caused the vena cava to collapse around the venous cannula, the system went from being compliant, with the patient essentially being a collapsible bag, to the venous line becoming a fixed volume container. As the siphon created a negative pressure, significant levels of out gassing were shown and replicated in human studies.

Further research is needed to better define the relative contribution of each of the "improvements" brought online by industry and academic investigators. We must continuously question how and why we perform certain actions and whether they are habits from early training that may not be appropriate today.

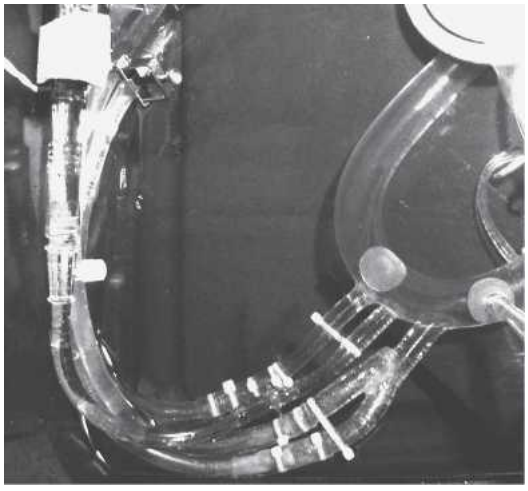

Figure 3. EDAC transducer positioned on simulated left carotid.

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Impact of Oxygenator Characteristics on Its Capability to Remove Gaseous Microemboli

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Abstract: Since the advent of cardiopulmonary bypass, the generation and elimination of gaseous and solid (micro) emboli have been a concern. Major improvements with respect to gaseous microemboli have been made by the introduction of arterial line filtration and membrane oxygenators. Animal experiments have shown a clear correlation between massive air embolism and outcome. However, limited knowledge is available regarding the cut-off point between the occurrence of negative outcome and the number and size of gaseous microemboli. Generation of gaseous microemboli can occur when using cardiopulmonary bypass. However, no consensus exists on when a given diameter or number of emboli becomes injurious to the patient. An important variable is the gas mixture inside the bubble. Nitrogen has a very long dissolution time that results in a prolonged ischemia for tissue behind the occlusion. The pathophysiologic reaction of the body when exposed to gaseous microemboli is most likely based on ischemia caused by partial occlusion of blood vessels and by endothelial damage. Gaseous microemboli can be cleared mechanically by using filters, by reduction of blood velocity, and by rapid reduction of the nitrogen content. Elimination of gaseous microemboli is dependent on the design of the cardiopulmonary bypass circuit. A membrane oxygenator, although not designed for it, can remove gaseous microemboli. Arterial line filtration is not the best solution for removal of gaseous microemboli, because larger emboli have been fractionated before reaching the arterial filter. Venous line filtration is a more efficient way for clearing gaseous microemboli. **Keywords:** gaseous emboli, oxygenators, CPB circuits. *JECT. 2007;39:271–273*

INTRODUCTION

Since the start of cardiopulmonary bypass (CPB), there has been some concern regarding solid and gaseous (micro)emboli. Of course at that time, the components of the CPB circuit were less efficient than today's equipment (1). Indeed, the transition from bubble oxygenators toward the existing extraluminal flow hollow fiber oxygenators has not only reduced the number of adherent thrombi from 25% to <0.3% (2), but also has reduced the number of gaseous microemboli (3–5). Better control or avoidance of cardiotomy suction has decreased drastically the number of solid and gaseous emboli generated by CPB (6–8).

To control the excessive solid and gaseous microemboli generation of bubble oxygenators, arterial filters were introduced in the 1970s (9). However, the largest progress in gaseous microemboli reduction was made with the introduction of the membrane oxygenator as it controlled the generation of gaseous microemboli. Nevertheless, gaseous microemboli are still generated in the existing systems, and further research is necessary for elucidating the origin of these microemboli and to new techniques for clearing them out of the circuit (10–12).

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ORIGIN AND PHYSICS OF GASEOUS MICROEMBOLI

Under normal conditions, no gaseous microemboli are present in the bloodstream. Gaseous microemboli can be generated when an extracorporeal circulation is used or when blood vessels and/or heart are opened for a surgical procedure. Also, perfusionist interventions can generate gaseous microemboli (13,14). Gaseous microemboli can consist of nitrogen, oxygen, carbon dioxide, or a mixture of these gases. Although a lot of research has been done on decompression sickness in divers, the underlying mechanisms of air embolism–induced injury are still not completely understood. One hypothesis proposes that the lodging of microbubbles in the microcirculation occludes flow and induces transient local ischemia (15). Other possible explanations are that the endothelium is activated and damaged by the microemboli or that the thromboinflammatory reaction occurs between the foreign surface of the microemboli and blood proteins and platelets. The latter happens over a longer time period than transient

ischemia, and both mechanisms may play important roles in air embolism (16). An additional problem, when gaseous microemboli are generated, is the fact that there will be a dynamic constant process of small bubbles fusing to create large bubbles and large bubbles splitting into many small bubbles; thus, a few "harmless" microbubbles could coalesce into one larger injurious bubble (17).

Once gaseous microemboli are present in the circulation, absorption from gas out of the microemboli into the bloodstream and the surrounding tissue will start. The absorption rate of gas out of the microemboli depends on the arterial nitrogen content, temperature, regional blood flow, and size of the gaseous microemboli. For bubbles <50 μm, absorption times are relatively short (≤2 minutes), so primary ischemia injury to the organs seems unlikely (18). However, larger microemboli are more likely to cause primary ischemic injury because of their longer absorption times. For the latter, interventions that substantively reduce absorption times will be beneficial in ameliorating neurologic outcome. The most effective strategies are those that reduce the arterial nitrogen content (19,20).

METHODS FOR REMOVING GASEOUS MICROEMBOLI

The most efficient technique in removing gaseous microemboli is preventing gaseous microemboli from being created. This can be done by optimizing circuit design (10) and assuring the air tightness of venous vascular access (21). Once gaseous microemboli are entering the extracorporeal circuit, the most efficient removal is realized at those locations in the circuit where a low blood velocity and thus high buoyancy exists. In practice, this is the venous reservoir. However, the fluid dynamics characteristics of a given reservoir and the average height of the blood column in the reservoir will influence its final removal efficiency (7).

Another component in the circuit helpful for removing gaseous microemboli is the arterial filter. All clinical filters used today are screen filters; thus, their basic working mechanism relies on a critical bubble point pressure. This also means that the smaller the pore size of the filter, the more efficient the filter will be in removing microemboli. However, microemboli with a size smaller than the nominal pore size of the screen will pass the filter screen (8). A more efficient filter, with respect to the clearance of gaseous microemboli, was the old Swank filter that was a combination of depth and screen filter. The effectiveness was explained by the fact that the filter medium also allowed interception and adhesion of smaller gaseous microemboli. For the very same reason, leukocyte removal filters are very effective in the removal of gaseous microemboli. The major disadvantages of screen filters are that they only work efficiently with an open shunt line, necessary for removing the captured emboli, and that there is an inverse relationship between the gaseous microemboli–removing efficiency and damage to cellular blood elements.

Finally, the oxygenator is capable of removing gaseous microemboli, although not specifically designed for it (22). The working mechanism is based on the reduction in blood velocity and the contact time with microporous hollow fibers. Also, the composition of the ventilating gas and the transmembrane pressure drop will influence the absorption rate in a microporous membrane oxygenator. However, a major disadvantage of today's oxygenators is the fact that the microemboli must first pass the heat exchanger in which they are fractionated in smaller bubbles (23). The very small mass of these fractionated microbubbles makes them very difficult to remove. Recent research has shown that the best technique for the removal of gaseous microemboli is using venous filtration or a venous bubble trap, because this will avoid further fractionating of the gaseous microemboli (24,25).

DETECTION OF GASEOUS MICROEMBOLI

The detection of gaseous microemboli during CPB remains a critical issue. Most devices use ultrasound for gaseous microemboli detection as this technology allows measurement in nontranslucent fluids and does not harm tissue or cellular blood elements. However, this technique has vulnerabilities. It is not able to measure microemboli less than a diameter of 10 μm. Devices may become saturated when larger amounts of gaseous microemboli are presented to the sensor, especially at higher flow rates. Indeed, a recent study showed a lot of shortcomings in one of the more popular devices and concluded "it seems impossible to resolve all these sensor-related problems by ever-increasing mathematical intervention. We believe it is more appropriate to develop a new kind of ultrasound device, free of these shortcomings. This seems to be particularly useful, because the problem of determining the size of gaseous bubbles in extracorporeal circulation (ECC) is not yet solved" (26). Recently, newer devices have been introduced into the market with a better reproducibility. However, until today, no validation of these devices under controlled circumstances has been performed.

CONCLUSIONS

The exact relationship between the number and size of gaseous microemboli and neurocognitive outcome is not yet clearly defined. However, generation of gaseous microemboli seems to be linked to the design of the CPB circuit (10), use of cardiotomy suction (7), use of vacuum-

assisted venous return (VAVD) (26–28), and the type of oxygenator (22).

Removal of these gaseous microemboli can be achieved by the venous reservoir, venous filtration, the oxygenator, and the arterial filter. However, the design and the fluid dynamics in all these components will determine the overall removal capacity of a given system.

Although several devices exist for the detection of gaseous microemboli, few of them have been validated under controlled conditions. Further research is necessary to determine the impact of bubble size and bubble count in the pathophysiology of gaseous microembolization.

Although many strategies can be followed after air embolism (29), for gaseous microemboli, the most efficient clearance is obtained by rapid reduction of nitrogen content (19).

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Large Multicenter Trials: What Do They Achieve and What Should Be Done in Perfusion?

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Abstract: There have been a vast number of publications in the perfusion and cardiac surgical literature suggesting possible therapeutic benefits from many perfusion interventions. Most of the reports are case series and other observational studies; few are randomized trials, and most of these are small, focusing on surrogate endpoints. We know there are many factors that can affect outcome after cardiac surgery, and some of these can bias results of clinical studies. Evidence-based medicine has highlighted the importance of avoiding bias with good study design, critical appraisal, and careful application into clinical practice. Associations shown in observational studies do not provide reliable evidence of effect (causation). Random allocation to treatment groups accounts for many sources of bias, but small randomized trials can still be unreliable because they may identify a spurious positive finding by chance (type I error), as well as providing imprecise estimates of effect, as shown by wide confidence intervals. Obtaining data on actual outcomes with enough study power requires a large number of patients. Meta-analysis of small randomized trials can increase power, but this introduces other sources of bias. Large randomized pragmatic trials, using straightforward interventions reflecting routine clinical practice, can optimize the ability to generalize and therefore are clinically relevant and reliable. They thus provide the best evidence of effectiveness. *JECT. 2007;39:274–277*

BEWARE OBSERVATIONAL STUDIES

A confident demeanor is a valued element of being a good clinician, but in reality, we practice in an environment of great uncertainty. Individual patient and clinician characteristics, and a whole host of perioperative factors, can affect outcome after cardiac surgery. Similarly, interpretation and clinical application of published research is hindered by uncertainty because of numerous alternative explanations of observed findings: is a positive result "true" or is it a spurious finding? Evidence-based medicine has highlighted the importance of avoiding bias with good study design, critical appraisal, and careful application into clinical practice (1). Many sources of bias have been known for a long time (2), but others have become more widely recognized because of new study design techniques (3,4).

Large case series, registries, and other prospective observational studies can provide a lot of useful data concerning patient and surgical characteristics and their relationship with patient outcome. Being large, such studies can provide sufficient power to identify possible associations between many specific factors and complications, and so it is a useful first step when studying potential improvements in care. However, strong associations have many possible explanations (2,4).

An illustrative example in perfusion is the relationship between red cell transfusion and poor outcome after coronary artery bypass graft surgery (CABG) (4). A large observational study in 11,963 patients undergoing CABG, in which one half had received a transfusion, found that red cell transfusion was associated with an increased risk of numerous serious postoperative complications. This included renal failure [odds ratio (OR), 2.1; 95% confidence interval (CI): 1.9–2.3; $p < .001$], serious infection (OR, 1.8; 95% CI: 1.7–1.8; $p < .001$), cardiac complications (OR, 1.6; 95% CI: 1.5–1.6; $p < .001$), neurologic events (OR, 1.4; 95% CI: 1.3–1.4; $p < .001$), and death (OR, 1.8; 95% CI: 1.7–1.9; $p < .001$). These associations persisted after accounting for patient and perioperative factors. Also, there was a clear dose response shown with each unit of red cells transfused being associated with an incrementally increased risk for complications (5). However, does this mean that red cell transfusion increase death and disability after CABG? Should we restrict red cell transfusion in this setting? Such studies have led to calls for restrictive transfusion practices and in particular use of a transfusion protocol (5), but there is no compelling evidence that this will reduce complications after CABG. There are many possible explanations for the observed association between

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red cell transfusion and poor outcome (4). Some can be tested and/or controlled for with multivariate analyses, but experience has taught us that these cannot be depended on (6,7). Associations shown in observational studies do not provide reliable evidence of effect (causation). They are hypothesis-generating, and stronger levels of evidence should be sought (7).

STUDY DESIGN

Reliability, or precision, is important to clinicians because we want to know whether likely effects of any new treatment are clinically useful in any particular circumstance (7). If uncertainty exists, a change in practice is unlikely until further studies are done. These issues are highlighted when considering the potential benefits and risks of off-pump coronary artery surgery (OPCAB). Early reports and case series published in the early 1990s suggested OPCAB reduced complications traditionally associated with cardiopulmonary bypass (CPB). These positive reports fostered great interest in off-pump techniques, but many cardiac surgeons were cautious because of concerns about inadequate revascularization. At present, the key questions seem to be (i) does OPCAB improve postoperative outcomes, and if so, (ii) is there sufficient evidence to support more widespread use; but if not, (iii) what type of studies are required to provide compelling evidence? A similar series of questions surrounded warm heart surgery in the 1980s, with the eventual widespread use of 32–34°C for most routine cardiac surgery (8), and laser myocardial revascularization with the eventual decline in interest for the technique in most settings (9).

WHAT OUTCOMES SHOULD WE BE MEASURING?

Research in CPB and other perfusion techniques frequently uses surrogate endpoints—biochemical markers such as blood gases, electrolytes, and hematologic results, urine flow, myocardial ischemia, embolic load, and cerebral blood flow. Some of these have no meaningful relationship to "actual" outcomes of concern to patients (10).

Clinical researchers typically use surrogate endpoints because obtaining data on actual outcomes with enough study power requires a larger number of patients. It is common for there to be an underlying assumption that the surrogate endpoint relates directly to the actual outcome. For example, troponin release is a marker of myocardial damage and therefore is a surrogate marker of myocardial infarction (MI); similarly, for delta creatinine and renal failure, cerebral oximetry and stroke, embolic load and stroke, and so on. In some circumstances, this can be accepted, but in others, the relationship is more tenuous. Experience in other clinical settings tells us that studies showing a positive effect on a surrogate endpoint can be quite misleading when a definitive outcome study is done (11). Thus, there should be greater efforts at following up initial positive studies based on surrogate endpoints with true outcome studies.

Because serious adverse outcomes after surgery are rare, outcome studies need to be large. For example, the incidence of stroke, renal failure, or death after CABG is mostly <4%. Study power is determined by the number of trial events, and therefore, power can be increased by focusing on high-risk patients and/or by using a combined endpoint (7,12). Both these approaches have been used in the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial (13).

WHY DO LARGE RANDOMIZED TRIALS?

It is far simpler, and far more common, for large clinical studies to be observational (non-randomized), and therefore, they may be biased (2,14). We know outcome after cardiac surgery is dependent on many factors, and therefore a new treatment being studied may have a spurious association with a good outcome unrelated to any true effect. Random allocation to treatment groups accounts for many such sources of bias (7).

The major source of bias overcome by randomization is treatment bias, whereby allocation to treatment groups is not decided by the clinician or patient. However, small randomized trials can still be unreliable because they may identify a spurious positive finding by chance (type I error), as well as providing imprecise estimates of effect, as shown by wide confidence intervals (7,8). For example, a small randomized study in 80 patients undergoing CABG surgery compared on-pump and off-pump CABG (15). Myocardial injury was assessed using serial troponin release, and this was significantly lower in the OPCAB group for up to 24 hours postoperatively. In addition, inotropic requirements were less in the OPCAB group, but this did not reach statistical significance. These findings offered promise but do not convincingly show improved outcome (less myocardial injury or deaths) with OPCAB.

Another small trial addressed the effect of OPCAB on long-term graft patency in 197 patients (16). Graft patency was similar for OPCAB and conventional CABG using CPB at 30 days ($p = .19$) and at 1 year (absolute difference, –2.2%; 95% CI: –6.1% to 1.7%; $p = .27$). Rates of death, stroke, myocardial injury, and reintervention were also comparable. The authors concluded that OPCAB provided comparable rates of complete revascularization and was cost effective (16). Is this enough to change practice? Given that the author had extensive experience in OPCAB surgery, does this allow an ability to generalize to other settings? Do the 95% CIs suggest a clinically important increase or decrease in graft patency, myocardial in-

jury, or death? For example, the risk of death was slightly higher in the OPCAB group, but this was not statistically significant (OR, 1.6; 95% CI: 0.3–9.8). Would a 1.6-fold (or 9.8-fold) increase risk of death temper enthusiasm in OPCAB? If the study was multicenter (numerous surgeons and settings), and the outcomes being studied were myocardial injury, stroke, and death, a change in practice would be justified. To be fair to the authors of this study, it was not their stated intention to address these latter issues. However, that is what is required to change practice (17).

Small trials are still prone to imbalances in prognostic factors that can have a potent effect on outcome: a special type of bias known as confounding (7,18). The larger the sample size in a randomized trial, the less likely it is that confounding can occur. A large randomized trial will equalize both known and unknown confounders between groups (6,7). Large trials are usually multicentered, and sometimes multinational, to maximize recruitment and enable early conclusion (6,7). This provides a broad range of settings and offers an opportunity to identify other patient, clinician, and institutional factors that may influence outcome. Large trials with straightforward requirements reflecting standard practice are sometimes called effectiveness, pragmatic, or practical trials (6,17). They thus optimize the ability to generalize their findings and therefore are clinically relevant. This is often not the case, with interested researchers studying select groups of patients in specialized settings. This is particularly relevant in perfusion studies, including use of off-pump surgical techniques, because of specific expertise at some centers—positive results may not be reproduced in other settings.

Another area of interest to perfusionists is neurologic injury associated with CPB, and in particular, stroke. A small trial reported a reduction in cognitive deficits with OPCAB at 3 months but no difference at 6 months after surgery (19). There were no significant differences in stroke or death rates, but the study was not designed or adequately powered to reliably address these issues. Several other trials have been done on this topic, and therefore, a pooled analysis can be done. This increases sample size and therefore increases study power. Such meta-analyses can provide least-biased estimates, but there are some weaknesses with this approach, particularly when meta-analysis is limited to small trials (20,21).

Sedrakyan et al. (22) identified 41 trials of OPCAB that had enrolled 3996 patients and reported a 50% reduction in the relative risk of stroke (95% CI: 7%–73%), 30% reduction in atrial fibrillation (95% CI: 16%–43%), and 48% reduction in wound infection (95% CI: 26%–63%). These studies represent a diverse range of clinical settings. Here, for the first time, we have strong evidence that OPCAB can significantly reduce serious complications associated with CPB. The outcomes are serious and have a real impact on patient's lives. This evidence might affect a surgeon's practice, but the authors caution overinterpretation because of limitations of meta-analyses, variations in surgical expertise, increased need for conversion to on-pump surgery, and a lack of long-term outcome data (graft occlusion and reoperation). The current state of evidence clearly supports a definitive large randomized trial comparing OPCAB and on-pump CABG with short-term and long-term follow-up.

What should be done to improve the evidence base of perfusionist practices? Collecting accurate perfusion and perioperative data is a good first step. Ideally such data collection should be coordinated and extensive (multicenter), using agreed data definitions. Considering possible improvements in care (from such data or from any positive publications) should lead to testing new interventions with randomized trials. Irrespective of the size of the clinical trial, meaningful outcome data should be routinely collected and reported (to enable meta-analyses), and definitive large trials should eventually be done. Large trials rightly deserve the mantle of "gold standard" in providing evidence of effectiveness, because they provide reliable and relevant information to guide clinical practice (6,17,23,24).

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What Is Optimal Flow and How to Validate This

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Abstract: Since the introduction of cardiopulmonary bypass, clinicians have tried to define the optimal blood flow for a given patient. The difficulty in determining a correct blood flow lies in the fact that cardiac surgery is done in a very inhomogeneous population, from neonates to the octogenarian, and often under non-physiologic conditions (hypothermia, hemodilution, low flow, etc.). Although clinicians acknowledge that maintaining a minimum oxygen delivery is more meaningful than using a fixed flow rate based on the metabolic needs of awake resting volunteers, the latter is most used in clinical practice. This is explained by the fact that no values are available on critical oxygen delivery for adequate tissue oxygenation under a given clinical condition. This was an overview of the relevant literature. In most centers, perfusionists use in-line monitoring, such as venous saturation or venous blood gases, for estimation of adequacy of tissue perfusion. Unfortunately, these oxygen-derived parameters have a poor correlation with anaerobic energy supply. Measurement of intermittent whole blood lactate concentration is used to compensate for this poor relationship, but as it monitors the concentration at given time points, it precludes optimally timely intervention by the perfusionist. The physiologic buffering by bicarbonate of the acid generated by converting pyruvate into lactate will produce carbon dioxide. As a consequence, carbon dioxide–derived parameters do have a good correlation with inadequate tissue perfusion. In-line monitoring of carbon dioxide production gives real-time information on tissue perfusion. Use of a standard reference flow for each patient is a poor option, because it does not reflect the metabolic need of the patient. Oxygen-derived parameters, such as venous saturation or partial venous oxygen tension, are poor predictors of anaerobic metabolism. A combination of intermittent whole blood lactate measurement with carbon dioxide–derived parameters predicts anaerobic energy production and allows proactive intervention by the perfusionist. **Keywords:** cardiopulmonary bypass, tissue perfusion, blood flow. *JECT. 2007;39:278–280*

INTRODUCTION

In humans, cardiac output is regulated based on metabolic needs. The basal cardiac output is between 2.8 and 3 L/m^2/min but can increase up to 15 L/m^2/min during exercise. However, when a patient is placed on cardiopulmonary bypass (CPB), this delicate metabolic balance is disturbed. Instead of being controlled by a metabolic feedback system, cardiac output will now be determined by the perfusionist, who has to decide the ideal cardiac output for a given condition. Determination of the correct blood flow is difficult because judgment needs to be made on derived and calculated parameters because very little direct information regarding the adequacy of tissue perfusion can be obtained during CPB. Also, during CPB, non-physiologic conditions that occur such as hemodilution and hypothermia further impact flow requirements. Because of these difficulties, many perfusionists use standard blood flows. Most perfusionists will use flows of 2.2–2.8 L/m^2/min (1). These reference values were obtained by measuring blood flows in resting non-anesthetized, healthy volunteers. We will study whether these standard flows really cover the metabolic needs of patients during the different phases of CPB.

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DETERMINANTS OF CARDIAC OUTPUT

Cardiac output is defined as the volume the heart (or during CPB, a pumping system) can deliver per minute, but this value does not mean anything in isolation. What is of real interest is the amount of oxygen that can be delivered to the tissues. Oxygen delivery depends on the cardiac output and the oxygen content per liter of blood. Thus, it would make much more sense to try to determine the optimal oxygen delivery for a given condition. Doing so would also put hematocrit and thus hemodilution into the equation.

Recently, several large randomized studies showed a correlation between the lowest hematocrit on bypass and the incidence of postoperative renal failure (2–7). The reason of this correlation is most likely because of the fact that the medullar portion of the kidney is at particular risk for low oxygen status. Ranucci et al. (7) clearly showed

that augmenting blood flow could markedly ameliorate the negative relationship between hematocrit and the occurrence of renal failure. Their conclusion was that it was not the hematocrit value in itself that was the main cause of the renal failure but that it was more dependent on a critical oxygen delivery. They found the critical oxygen delivery to be 272 mL/min/m^2. This finding makes it possible to abandon reference blood flows and to replace them with critical oxygen delivery values. This approach makes it also possible to actively modulate the incidence of CPB-associated morbidity.

PARAMETERS OF ANAEROBIC METABOLISM

Under normal resting conditions, oxygen delivery matches the overall metabolic demands of the organs; oxygen consumption by the body is ~25% of the oxygen delivery. Under these conditions, energy production is almost completely aerobic. However, this situation will change drastically whenever oxygen delivery is jeopardized by low cardiac output or reduced arterial oxygen content. Because of the high reserve oxygen content of normal oxygen delivery, small reductions in oxygen delivery will not affect oxygen consumption, but once a critical oxygen delivery is reached, oxygen consumption starts to decrease as it becomes dependent on oxygen delivery. To produce sufficient energy, the failing aerobic energy supply will now be expanded with anaerobic energy production through pyruvate conversion to lactate.

As a direct consequence of anaerobic metabolism, blood lactate concentration starts to rise. Lactate concentration can be considered a good marker of non-optimal tissue perfusion (8). Once the anaerobic metabolism comes into play, increased proton production will lead to tissue acidosis. The physiologic buffering of these protons with bicarbonate will lead to anaerobic carbon dioxide production (9). In a situation where oxygen supply is no longer sufficient for aerobic energy supply, there will be a linear decrease in oxygen consumption and thus also in carbon dioxide production, but at the same time, there will be carbon dioxide production from the anaerobic energy production. As a result, the net carbon dioxide production will rise, and the respiratory quotient will increase (10). In a state of cardiogenic shock, the increased carbon dioxide produced can no longer removed by the natural lung because pulmonary blood flow will also be reduced in shock. Because of this, there will widening of the partial carbon dioxide tension gap between arterial and venous blood.

ESTIMATE OF ORGAN PERFUSION DURING CPB

To validate the quality of perfusion and to estimate tissue oxygenation, perfusionists use several approaches including commonly used in-line measurements of venous saturation and blood gases. Unfortunately, venous saturation and venous partial oxygen tension are an indirect reflection of tissue oxygenation, and a high venous saturation/venous partial oxygen tension does not preclude that one or more organs are not optimally perfused. Indeed, several studies have shown that oxygen-derived parameters are poor in predicting lactate accumulation during CPB (11).

Therefore, the question remains of how one could or should effectively monitor tissue perfusion and oxygenation during CPB. In small children, the introduction of near infrared spectroscopy (NIRS) of both the cerebral circulation and the kidney has been shown to be very helpful for the rapid detection of perfusion maldistribution in complex congenital corrections such as the Norwood procedure (12). In an adult population, less conclusive evidence is available to support the routine use of NIRS. This can be explained in part by the fact that an adult population will not only have a cardiac pathology, but in the majority of cases, also a pronounced atherosclerosis of the complete vascular tree. Also, associated morbidity can severely jeopardize perfusion adequacy of a given organ(s). However, a recent prospective randomized study in a patient cohort of 200 patients showed a significant benefit in patient outcome in the group where NIRS was used to evaluate cerebral desaturation (13).

Another approach is to measure at given time intervals the lactate concentrations in whole blood. This technique is used more and more as a standard approach in European hospitals because lactate electrodes are now standard on most blood gas analyzers. Over the years, many authors have studied the evolution of lactate during CPB (14–18). In the literature, anaerobic energy production, validated by an increased lactate concentration, is found in up to 20% of all patients during CPB (19). Most authors could find a positive correlation between increased lactate concentration and duration of aortic cross-clamp, duration of CPB, and hemodilution (8,10,15). However, a major disadvantage of this approach is that it monitors the evolution of lactate accumulation but does not permit timely intervention.

Recently, Ranucci proposed continuous monitoring of carbon dioxide–derived parameters for rapid detection of anaerobic energy supply (10). Today's microporous hollow fiber oxygenators are extremely efficient in removing carbon dioxide. Indeed, perfusionists who routinely measure gas exhaust carbon dioxide tension observe an almost immediate increase in capnographic values when they administer bicarbonate ions or packed red cell concentrates. Because of this high efficiency, the oxygenator is, in contrast to the natural lungs, better at removing excess carbon dioxide produced by the anaerobic metabolism. As a consequence, widening of the arterio-venous partial carbon

dioxide tension gap reflects anaerobic carbon dioxide production with a critical oxygen delivery will be reflected during CPB by an increase in capnographic values. Carbon dioxide–derived parameters were more efficacious compared with oxygen–derived parameters in predicting lactate accumulation during CPB (11). The best indicator was the ratio between oxygen delivery and carbon dioxide, followed by carbon dioxide production, and then by the ratio between carbon dioxide production and oxygen consumption (10). All indicators were normalized for body surface area.

CONCLUSIONS

A reference flow, as used in many centers, is no guarantee of an adequate tissue perfusion. A minimum oxygen delivery is a better reflection for satisfying a given metabolic need. However, validation of critical oxygen delivery is necessary. Oxygen-derived parameters such as venous oxygen saturation and venous partial pressure are poor predictors of tissue perfusion. Measurement of local oxygen consumption by NIRS in children or continuous measurement of carbon dioxide production in adults is a more sensitive indicator of inadequate tissue perfusion. Carbon dioxide–derived parameters in combination with intermittent whole blood lactate levels provide inline information regarding tissue perfusion, allowing the perfusionist to proactively intervene to optimize tissue perfusion during CPB.

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Why the Inflammatory Response Is Important to the Cardiac Surgical Patient

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Abstract:
Although the systemic inflammatory response is recognized to contribute to patient morbidity and mortality after cardiopulmonary bypass, specific mechanisms linking cause and effect—linking a specific mediator with a defined adverse outcome—are lacking. The problem is partly because of the rarity of hard endpoints (stroke, myocardial injury, renal failure requiring dialysis), which studies are not always powered to measure, and partly one of definition; "systemic inflammatory response" wrongly suggests that the problem is confined to inflammation, whereas, in fact, it is characterized by systemic disturbances to a number of the body's natural defenses against injury and infection: fibrinolysis, coagulation, complement activation, immune cell activation, and oxidative stress in addition to inflammation. A better definition would be to think in terms of a "systemic host response" to surgery. End-organ injury results from the interplay of activated host defense systems with regional vessel wall injury, either because of physical trauma to the vein graft or ischemia/reperfusion injury to susceptible vascular beds. Improved patient outcomes are going to take a concerted team effort to achieve, from the point of atraumatic vein harvest, to improved biocompatibility and shear resistance of circuits, monitoring, and minimizing of ischemia to organs, minimal cross-clamping trauma, optimized blood management, and combinatorial drug strategies. Surrogate endpoints for major organ dysfunction will play an important role to make sense of multiple interventions by the cardiac surgical team and to monitor continuous improvement to patient outcomes. **Keywords:** cardiac surgery, inflammation, bypass. *JECT. 2007;39:281–284*

A PROBLEM OF DEFINITIONS

Just like most articles on the inflammatory response to cardiopulmonary bypass (CPB), this article begins with a woolly sentence linking the systemic inflammatory response to morbidity and mortality. The woolly phrases betray our lack of clarity and understanding of the mechanisms that link cause and effect—that link inflammation with a defined outcome.

The problem, in part, is one of definition: "systemic inflammatory response" makes us think about a catalog of cytokines and chemokines that might be elevated in plasma after surgery; and the catalog has almost literally been thrown at the problem. However, we are talking about much more than just systemic mediators when we think about the morbid sequelae of cardiothoracic surgery and CPB to our patients; we are referring to a complex series of interactions, involving major perturbations to the coagulation, fibrinolytic, complement, and immune pathways of activation that conspire to produce an adverse outcome. Typically, adverse outcomes linked to the systemic inflammatory response are defined by soft endpoints, such as quality-of-life indicators, hospital stay, or organ dysfunction defined in variable ways (e.g., neurocognitive decline). Hard endpoints, such as death, myocardial infarction, stroke, or renal failure requiring dialysis are thankfully rare, but their rarity makes categorical linkage between cause and effect very difficult. Most intervention studies are inadequately powered to detect hard endpoints in isolation.

A more holistic interpretation of the body's response to cardiac surgery is needed: a better definition might be to describe it as the "systemic host response" to surgery. Such a nomenclature would help us understand that there are multiple interlinked components of the response and that successful intervention may require more than one angle of interdiction.

HOST DEFENSE SYSTEMS ACTIVATED BY CARDIOTHORACIC SURGERY WITH CPB

This article will confine itself to a consideration of cardiothoracic surgery with CPB. As shown in Figure 1, such surgery throws into disequilibrium many of the body's

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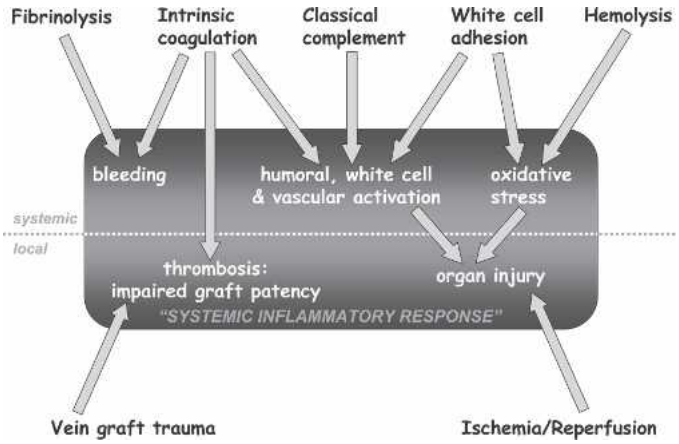

Figure 1. The systemic inflammatory response is actually a composite of host defensive responses activated during cardiothoracic surgery with CPB; these combine to produce systemic and local complications postoperatively. Passage of blood over the artificial surfaces of the bypass circuit activates fibrinolysis, intrinsic coagulation, classical complement, white cells, and platelets and leads to hemolysis. These systemic insults lead to systemic complications, such as excessive bleeding, inflammatory activation of humoral, cellular, and vascular components of the immune system, and oxidative stress. Localized injury can manifest either as organ injury, because of a combination of systemic insults and regional ischemia/reperfusion, or impaired graft patency because of systemic thrombin production. The molecular details of the pathways that comprise the systemic inflammatory response are discussed in the text.

natural defense systems against injury and infection, leading to systemic and local complications.

FIBRINOLYSIS AND COAGULATION

Among the pathways activated by passage of blood through the extracorporeal circuit is fibrinolysis. This is a negative feedback pathway designed to prevent fibrin-rich occlusive thrombi from forming during the host response to injury (1). Fibrinolysis is strongly activated during cardiothoracic surgery with CPB, leading to the breakdown of fibrin into D-dimers catalyzed by plasmin (2). Fibrinolytic activation secondary to plasmin generation during bypass is a major cause of surgical bleeding. Intrinsic coagulation is another pathway that is sent into shock after surgery, with large amounts of thrombin generated in the bypass circuit despite adequate heparinization (3,4). The intrinsic coagulation pathway is designed to generate finely calibrated amounts of thrombin after injury, sufficient to initiate hemostasis but not enough to cause thrombus formation (5). Uncontrolled thrombin generation in the bypass circuit carries with it a prothrombotic risk to the grafted vessel, as well as a paradoxical bleeding risk systemically. The systemic bleeding risk is caused by consumption of clotting factors (consumptive coagulopathy) and the unwanted activation of platelets by thrombin in the bypass circuit (6). Thrombin desensitization of platelets is the main cause of the clinical platelet deficit recognized in CPB surgery, and this will be discussed in greater detail in a companion article (7). Coagulation factors such as kallikrein and thrombin can also activate vascular endothelium and white cells, thus explaining some of the febrile and capillary leak symptoms seen in CPB (8–10).

COMPLEMENT AND IMMUNE ACTIVATION

The complement pathway is another of the body's defense systems against infection engaged during CPB. IgM and IgG antibodies are deposited onto the extracorporeal circuit and trigger the classical pathway of complement activation (11). Vasoactive factors C3a and C5a can activate white cells and endothelium, thus combining with coagulation factors and cell adhesion pathways to cause systemic inflammation and permeability changes to blood vessels.

An often overlooked pathway of white cell activation is direct cell adhesion to the plastic surfaces of the bypass circuit. Binding of plastic engages the same adhesion receptors as are used for phagocytosis of bacteria, notably the complement receptor, CR3 (also known as Mac-1 or $\alpha_m\beta_2$ integrin). In fact, cell adhesion to plastic has been dubbed "frustrated phagocytosis" (the cell trying to phagocytose the whole plastic circuit) and is linked to the same cytodestructive inflammatory cytokine, protease, and reactive oxygen release as occurs during genuine phagocytosis by neutrophils and macrophages (12,13).

END-ORGAN INJURY

End-organ injury results when one or more of the systemic pathways activated during surgery synergizes with localized trauma to the grafted vessel or to vascular beds susceptible to ischemia/reperfusion injury. Careful and insightful work in the setting of off-pump surgery has shown that the only independent predictor of saphenous vein graft failure is endothelial denudation of the grafted vessels (14,15). This makes teleologic sense, because the two surfaces of the intrinsic and extrinsic pathways (platelets and tissue factor bearing cells of the subendothelium) are now brought into contact, with the inevitable propagation of a fibrin and platelet-rich thrombotic clot (1,5). Atraumatic vein harvest, gentle manipulation during surgery, and minimal cross-clamping force should be seen as absolutely essential measures to minimize the risk of graft occlusion and myocardial injury (14,16).

The many systemic host–response pathways activated during surgery may also synergize with ischemia/reperfusion to promote attachment and transmigration of harmful leukocytes into susceptible organs, such as the brain, lung, heart, and kidneys, with tissue injury resulting from the release of cytodestructive mediators (17–19). Put more lucidly by Professor Ken Taylor from the Hammersmith Hospital, UK, in a recent British Broadcasting Cor-

poration interview: "The white cells of the immune system are all too aware of the differences between real blood vessels and the tubes of heart lung machines. . . . they immediately recognize these materials as foreign, and react defensively, as though the body was under attack from an infection. When the stimulated white cells travel back into the body of the person undergoing heart-lung surgery, they cause inflammation which can seriously damage the brain, lungs, kidneys, and other organs."

A further source of oxidative stress and a possible cause of direct kidney injury is myolysis and hemolysis. "Crush syndrome" caused by myoglobin release from injured muscle tissue has been described in trauma victims and may contribute to nephrotoxicity in cardiac surgical patients (20). Probably of greater importance in the setting of cardiac surgery is intravascular hemolysis, caused by the shearing of erythrocytes in the bypass circuit, leading to the release of plasma-free hemoglobin (21–23). Among the body's many iron stores, the heme iron moiety is uniquely bioavailable for oxidative reactions when not safely compartmentalized within red blood corpuscles (24). Peak oxidative stress caused by hemolysis occurs at the time of cross-clamp release, earlier than the first detectable inflammatory cytokine generation (21–25). Free hemoglobin released into the bloodstream secondary to hemolysis can abrogate vasoprotective responses caused by nitric oxide and may accumulate in the proximal tubules, causing direct injury, especially in patients with diabetes (26–29). A significant contribution to the "systemic inflammatory response" may therefore be caused by oxidative stress and loss of vascular nitric oxide responses secondary to hemolysis; cardiotomy suction devices that cut down on hemolysis are being developed and could become an important way to protect patients from acute perioperative oxidative injury (30).

CONCLUSIONS

The multisystem etiology of the systemic inflammatory response described above should remind us to think of postsurgical complications in more holistic terms than merely a disorder of "inflammation"—it is better described as the systemic host response to surgery. Effective taming of this multifaceted host response will require the whole surgical team and a combination of interventions to stabilize the many systems and organs traumatized during surgery. Evaluating a multipronged intervention is going to be a challenge and may require use of surrogate endpoints or a sentinel organ, such as brain oxygen saturation (31), to monitor continuous improvements by the surgical team.

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Optimization of the Perfusion Circuit and Its Possible Impact on the Inflammatory Response

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Abstract: Although there has been a steady improvement in cardiopulmonary bypass (CPB) techniques since its early introduction, it is still associated with some morbidity. Further attenuation of bypass-related systemic inflammatory reaction demands multidisciplinary action because the basic physiopathology is complex and cannot be controlled by one approach alone. This is an overview of the literature. Introduction of "mini" CPB circuits makes it easier to compare perfusion outcomes between different centers. Indeed, these circuits have a comparable fluid dynamic characteristic and surface area. All of them have a hemocompatible coating, and the technique avoids return of the pleuropericardial aspirations into the systemic circulation. As a consequence, results are very comparable to those obtained by beating heart surgery. However, vascular access and the resultant change in flow pattern in the aorta still have a negative correlation with neurocognitive outcome. A better understanding of the delicate balance between fluid dynamics, foreign material, coagulation, and inflammation is still a major requirement, especially because recent research combining pharmacologic, surgical, and anesthesia techniques with perfusion techniques has shown attenuation of the inflammatory response sequelae. For example, a better neurologic outcome is achieved by combining separation of suction, reducing hemodilution, administration of high-dose aprotinin, and volatile anesthetics and alternative cannulation techniques. Further improvement of CPB requires more uniform CPB circuits with known characteristics. The design should be based on evidence-based medicine philosophy. Combined efforts should be made by anesthesiologists, perfusionists, and surgeons to attenuate contact activation, ischemia-reperfusion injury, blood–material interaction, cell damage, and neurocognitive outcome. **Keywords:** vascular access, shed blood, cell damage, inflammatory reaction. *JECT. 2007;39: 285–288*

INTRODUCTION

Although cardiac surgery with cardiopulmonary bypass (CPB) has resulted in an improved quality of life to millions of people over the last five decades, it remains associated with a variably pronounced inflammatory reaction. Until the end of the past century, most clinicians believed the main cause of this reaction was attributed to the use of CPB per se. However, the introduction of beating heart surgery showed that an important part of this inflammatory reaction is more related to surgery itself than to CPB. This report will focus on some aspects of the pathophysiology of CPB and on strategies by which one can modulate the systemic inflammatory response.

HEMODYNAMIC CHANGES

Before starting CPB, one has to establish vascular access. This means that a rigid system, being the CPB circuit, is branched to the elastic compliant vascular system. The relative small aortic cannula delivers a high-velocity turbulent blood flow in the aorta (1,2). Depending on the insertion site of the cannula, this can result in the inverse rotation of the blood flow into the aorta (3). The high velocity created by the aortic cannula may "sand blast" the aortic wall and can lead to organ embolization (4,5).

After cannulation of the great vessels and institution of extracorporeal blood flow, major changes will occur. The blood from the venous circulation is drained into the circuit and, as an immediate result of this action, the output from the native heart is reduced or abolished. Because the heart is a pulsatile pump, this leads to a reduced or absent pulse pressure in the vascular tree. Finally, the shunting of blood toward the venous reservoir will reduce blood flow through the pulmonary circulation.

The obliteration of pulse pressure in the systemic circulation has a major impact on organ and tissue perfusion, because the shear forces generated by the pulsatile flow are mandatory for endothelial-derived nitric oxide generation. The reduced lung flow will attenuate the clearance of the bradykinin generated by contact activation (6). Indeed, the majority of angiotensin-converting enzyme re-

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ceptors are located in the lung vasculature and thus are bypassed when CPB is instituted. The latter is one of the causes of the hypotension observed after initiating CPB.

BLOOD–MATERIAL INTERACTION

When blood comes in contact with the different artificial surfaces of the CPB circuit, many reactions take place. First of all, there is an important contact activation that generates bradykinin, and the latter will stimulate in a dose-dependent manner the release of endothelial tissue plasminogen activator, the key enzyme in the initiation of fibrinolysis. At the same time, proteins are adsorbed by the mostly hydrophobic materials, and this activates the intrinsic coagulation cascade, blood platelets, and the complement cascade. As a result, thrombin will be generated, and white blood cells will first stick and subsequently migrate through the endothelium into the interstitium.

HEMOLYSIS

Hemolysis is defined as damage to blood elements, but in general, many clinicians will narrow this definition to damage to red blood cells. However, one could wonder if red blood cell destruction should still be our major concern in today's perfusion technology. Indeed, in most cases, the total amount of destroyed red blood cells will not exceed a few milliliters of blood and is thus negligible for oxygen transport. The largest part of that destruction is not caused by the CPB circuit but by aspirating pleuropericardial blood losses (7). However, free plasma hemoglobin remains important, because it is a potent antidote of nitric oxide and will induce pulmonary and systemic hypertension (8). In the literature, most authors are still using plasma free hemoglobin as a measure of red blood cell destruction. However, the same amount of cell destruction can give quite different values of free plasma hemoglobin (Hb) depending on the haptoglobin (Hp) phenotype of the patient. It would be better to state that hemolysis becomes more harmful the moment haptoglobin is no longer present for the formation of stable Hp–Hb complexes (9). These complexes will reduce the loss of Hb through the glomeruli, protect against peroxidative kidney injury, and allow the recycling of heme iron. Haptoglobin will also indirectly exert an anti-inflammatory reaction as the Hp–Hb ligand binding to CD163 on human monocyte–macrophage complexes will secret interleukin (IL)10 (10). Unfortunately, there is an overrepresentation of patients with haptoglobin phenotype 2–2 in cardiac surgery (11). Patients with this allele have the lowest binding capacity for free iron. The iron retention in Hp 2–2 individuals results in a degree of iron-driven oxidative stress, which is reflected by lower extracellular vitamin C concentrations (12), a powerful free radical scavenger and first-line antioxidant.

SUCTION BLOOD

During CPB, blood is often lost into the pleuropericardial cavities. Until recently, this blood was considered "safe" because it is anti-coagulated. However, recent research clearly showed that blood that has been in contact with damaged tissue is highly contaminated. Suction blood contains high levels of activated platelets represented by high plasma levels of PF4 and β-thromboglobulin (13). The high levels of PF4 inactivate the heparin in the blood, resulting in low anti-coagulation and high thrombin levels (14). The high levels of thromboxane can lead to pulmonary hypertension. Suction blood also has a high fibrinolytic activity (15) and has a negative impact on the coagulation potential of a given patient.

In addition to the above, the blood has high free plasma hemoglobin levels (7) and contains a high load of fat emboli (16). The latter has been increasingly implicated as one of the main causes of cognitive dysfunction after CPB. The fact that these fat emboli cannot be effectively removed out of the circuit with the existing filters makes it a serious problem.

HEMODILUTION

Hemodilution during CPB has been considered for years as beneficial because it counteracted the increased blood viscosity that occurred during hypothermia. However, recent work shows that there is an important relationship between hemodilution and morbidity (17–21). In adults, hematocrit levels < 24% are correlated with a higher incidence of acute renal failure. In pediatric surgery, better neurologic outcome is observed after deep hypothermic circulatory arrest when relatively high (±30%) hematocrit levels are maintained during bypass (22). According to some authors, worse outcome, when using low hematocrit levels during CPB, is more related to an insufficient oxygen delivery than to the hematocrit level per se (21). As a direct consequence, a low hematocrit level will not necessarily increase morbidity as long as sufficient oxygen delivery is maintained (e.g., by increasing blood flow).

When discussing hemodilution, one has to consider the different priming fluids. First, there is the choice between crystalloid fluids and plasma expanders (23). Buffered electrolyte solutions maintain better electrolyte homeostasis and acid–base equilibrium. The higher viscosity of plasma expanders will maintain a better microcirculation. Based on this, buffered gelatin solutions seem to be an excellent choice (24). Starches do have an impact on plate-

let function, but there is some evidence that they can attenuate the inflammatory reaction. Addition of albumin to the priming solution will passivate all foreign surface area and helps to enlarge the buffer capacity of plasma when hypothermia is applied (25). Finally, exclusion of glucose and the addition of mannitol into the priming solution have been shown to be advantageous (26).

THE CIRCUIT

One of the major disadvantages of CPB is the great heterogeneity in circuits between cardiac centers. As a direct consequence, it is very difficult to compare one center against another. The introduction of the so-called mini circuits does allow these comparisons because all systems are constructed the same way. Impact on morbidity of almost every component has been described in the existing literature. However, only in recent years has it become possible to evaluate the combined impact of different components used in the same manner and in large series.

CONCLUSIONS

Several strategies are available to reduce CPB-related morbidity, but it is quite clear that optimal modulation can only be achieved by combining different strategies.

A first strategy is pharmacologic intervention. Aprotinin has a beneficial impact on platelet function, contact activation, and thrombin generation (27–29). It attenuates the inflammatory reaction and can ameliorate neurocognitive outcome (29). However, recently there has been some debate regarding its safety (30). Pharmacologic inhibition of C5a and terminal complement complex looks promising, as shown by some pilot studies (31). Infusion of direct or indirect nitric oxide donors is a relatively simple method to compensate the loss of endogenous nitric oxide production during CPB. The use of methylprednisolone for control of the systemic inflammatory response remains more debatable in recent literature. Finally, the use of sevoflurane has shown to attenuate myocardial damage and to protect kidney function (32).

A second strategy focuses on the CPB itself. Blood–material interaction can be attenuated by the use of surface modification. Two major approaches are available. Heparin coatings are more beneficial for attenuating complement activation, whereas non-thrombogenic coatings are mainly preserving platelet function (33). However, return of pleuro-pericardial aspirations into the systemic circulation will blunt the beneficial interaction of a coating (34).

Returning blood aspirated from pleuro-pericardial cavities into the systemic circulation should be avoided as much as possible (13–16,34).

Pulsatile flow should be instituted whenever possible without charging the heart, because this will ameliorate tissue perfusion and help to control hypotension (6,35).

Finally, evidence-based medicine should help to define which are the most efficacious combinations.

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Deformable Emboli and Inflammation: Temporary or Permanent Damage?

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Abstract: Neurologic sequelae after cardiopulmonary bypass have a multi-factorial etiology. Although it is typically thought that a neurologic dysfunction means a focal lesion, symptoms of a brain disorder can be initiated by metabolic disruption such as from hyper- or hypoglycemia, hypercalcemia, renal and hepatic injury, fatigue, and anesthesia. However, one of the most important causes of acute neurologic dysfunction is edema. Brain swelling is associated with the systemic inflammatory response and the passage of deformable microemboli. The larger question is whether acute symptoms associated with brain swelling because of a breakdown of the blood–brain barrier contributes to a long-term negative outcome caused by cell loss. **Keywords:** cardiopulmonary bypass, microemboli, brain injury. *JECT. 2007;39: 289–290*

INTRODUCTION

Remarkable strides have been made in reducing death and stroke during and after cardiac surgery. As the etiologic factors associated with neurologic injury have been identified and eliminated, the patient's chance of escaping life-saving surgical intervention with an intact brain has greatly improved over the last decade.

However, although significant improvements have been made in the design of the extracorporeal circuits, cardiopulmonary bypass (CPB) remains associated with a risk for non–life-threatening neurologic complications. The injurious cascade related to CPB includes complement activation, adherent neutrophils, transmigration of leukocytes, production of oxygen-derived free radicals and proteolytic enzymes, embolic infarctions, and vasogenic edema, all of which possibly contribute to impaired neurobehavioral function postoperatively. However, emboli, both particulate and deformable, in the form of gaseous (1) and lipid microemboli, seem to be more of a major contributor to long-term neurologic dysfunction than previously appreciated.

The traditional view of how an embolus causes damage is by the occlusion of a vessel on the arterial side. The resultant lesion volume is affected by factors such as collateral circulation, capillary density, metabolic rate, and temperature of the ischemic tissue at the time of the occlusion. The key factor predicting the level of damage was presumed to be the focal cessation of flow to a fixed location, affecting a finite volume of tissue, in a specific arterial distribution and/or watershed area.

In an effort to describe the mechanism associated with ischemia/re-perfusion injury, most animals models of stroke or infarct revolved around stopping blood flow to a vascular bed by constricting a vessel using ligatures or floating a thread into a major vessel until it restricted downstream flow or even strangling the subject. What was seldom used in these experiments were actual emboli, or at least biologic emboli. These models are designed to eventually evaluate treatment strategies, as opposed to prevention of injury, the only adequate form of neuroprotection.

Microspheres have been substituted for biologic emboli for the purpose of causing a repeatable injury and volume of lesion. Of course, most of these studies are performed on young rodents with a perfectly smooth cortex, thus providing heuristic instead of practical insights into potential mechanisms of cerebral ischemia, at least in rats. The question has to be asked as to whether any of these models reflect real-life events in old people undergoing CPB.

The difficulty with most traditional models of embolization is that emboli behave differently depending, not only on their composition, but how they were manipulated before their delivery to a vascular bed. For example, normobaric microbubbles at normothermia will be absorbed according to the ideal gas law, but agitated, aspirated air bubbles in a protein bath (i.e., blood) will become "foam" with a lipoprotein sheath. Thus, an air bubble is transformed into a particulate embolus with a gas core and will not be absorbed until the sheath breaks down. Furthermore, the exact same embolus will behave differently in

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the gut, which has arterio-venous shunts, than it will in the cerebral vasculature, which has neither shunts nor a lymph system to remove metabolic waste. The brain does not have the ability to regenerate itself as do other organ systems, making cell loss secondary to microembolic insult a much more significant injury to the brain.

In a closed container such as the skull, the brain has a very limited ability to maintain adequate perfusion in the face of edematous challenge and an increase in intracranial hypertension. As deformable emboli transit, or are "extruded," through the cerebral circulation, the resultant breakdown of the blood–brain barrier (BBB) causes marked brain edema and cellular stress, as evidenced by heat shock protein and potential cell loss. Instead of an ischemic infarct, cell loss is initiated, which may eventually result in sufficient loss of mass that the ventricles will be noticeable enlarged (2). A generalized loss of brain mass will result in reduced brain function but not crisp, easily identified neurologic syndromes such as aphasia or a visual field cut.

BBB dysfunction has been suggested to be associated with the transient brain edema shown by magnetic resonance imaging after CPB and increased ventricular volume in long-term follow-up studies (2–5).

The BBB ensures an optimally controlled homeostasis of the brain's internal environment by regulating the transport of water, blood cells, and solutes through unique cerebral intercellular junctions: adherence junctions, tight junctions, gap junctions, and complexus adherentes. The passage, almost in the form of an extrusion, of microemboli through the vascular bed cause an endothelial disruption and initiate the inflammatory cascade. The final product is the loss of brain mass as damaged neurons die over the following months (2). This scenario potentially explains why patients often show acute symptoms that abate, but at the end of a year, these same patients are performing at a reduced level compared with patients who did not exhibit short-term deficits (6,7).

One of the consequences of the systemic inflammatory response to CPB is the activation of endothelial cells and their subsequent dysfunction (8). This process of endothelial dysfunction implies functional changes in the physiology of blood vessels, which may lead to problems of tissue perfusion. Of importance to the development of endothelial injury is the interaction between endothelial cells and neutrophils. After CPB, blood vessels are prone to leak. The resultant extravasation of fluid from the vascular compartment decreases shear forces within the blood vessels and increases contact between endothelial surfaces and circulating leukocytes. Because there are also increased levels of inflammatory cytokines and other vascular stimuli (e.g., complement anaphylotoxins, inflammatory lipids) in patients with atherosclerosis, both endothelial cells and leukocytes express cellular adhesion molecules on their surface. These adhesion molecules regulate the movement of leukocytes from the vascular compartment into the perivascular and interstitial compartments (9). Activated leukocytes further contribute to the endothelial injury by releasing oxygen radicals and degradative enzymes at the endothelial surface.

Our research suggests that to best protect the brain we must protect the endothelium. Traditionally, it is thought that an embolus must occlude a vessel to cause an ischemic infarct. Unfortunately, it is more complicated. We believe it is the interaction between the patient's preoperative endothelial health and intraoperative embolic events that precipitate the systemic inflammatory response, including breakdown of the BBB.

In addition, we have shown that gaseous and lipid microemboli can initiate endothelial dysfunction by being "extruded" through the microvascular bed. An activated endothelium is much more susceptible to injury. If a particulate embolus is captured earlier in its progression through a vascular bed, which has been activated by the previous passage of a deformable embolus, it will cause a larger ischemic lesion. The passage of microbubbles will initiate the adhesion of neutrophils in the capillary bed, which retard blood flow and substrate delivery. In addition to the transmigration of the leukocytes into the brain substance that cause brain swelling, the white cells are metabolically active and compete for a reduced supply of O_2 and glucose.

The only truly effective protection for the brain from the ravages of CPB-induced inflammation and microembolization is prevention through improvements in CPB technology and methods.

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Pharmacologic Strategies for Combating the Inflammatory Response

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Abstract: The "systemic inflammatory response" is a multifaceted defensive reaction of the body to surgical trauma and cardiopulmonary bypass (CPB), characterized by systemic activation of fibrinolysis, coagulation, complement, immune cells, platelets, and oxidative pathways, all overlaid onto localized trauma to the grafted vessel or vascular beds susceptible to ischemia/reperfusion. There is going to be no single magic bullet to diminish such a broad host defense response to surgery. The best chance lies with combinatorial—or promiscuous—pharmacotherapy. Combinations of anti-fibrinolytics, anti-coagulants targeted higher up the coagulation cascade, anti-thrombin receptor therapy, improved coated circuits, anti-complement, anti-leukocyte, and antioxidant therapies may blunt sufficient arms of the systemic inflammatory response to be clinically effective. The alternative is a promiscuous drug like aprotinin, which targets plasmin in the fibrinolytic pathway, kallikrein in the coagulation pathway, thrombin receptors on platelets and endothelium, and leukocytes at the extravasation step. Because of the overriding safety concerns relating to the use of anti-fibrinolytics in cardiothoracic surgery, any future combinatorial or promiscuous pharmacotherapy involving anti-fibrinolytics will require solid underpinning with a known mechanism of action and clinical safety data powered to detect well-defined adverse events (stroke, myocardial injury, renal failure requiring dialysis), preferably in isolation and not as a composite endpoint. **Keywords:** cardiac surgery, anti-inflammatory, antifibrinolytics. *JECT. 2007;39:291–295*

A MULTI-PATHWAY RESPONSE REQUIRES A MULTI-TARGET INTERVENTION

As discussed in the companion article "Why the inflammatory response is important to the cardiac surgical patient," cardiothoracic surgery with cardiopulmonary bypass (CPB) activates multiple host defense responses against injury and infection. Passage of blood through the extracorporeal circuit activates fibrinolysis, intrinsic coagulation, complement, white cells, platelets, and hemolysis. The term "systemic inflammatory response" does not do justice to the multi-system etiology of the body's response to surgery, which might be better thought of as a "systemic host response" to surgery. Systemic activation of host defense pathways directly or indirectly account for many clinical symptoms, including excessive bleeding, fever, and massive fluid shifts. Localized complications, like impaired graft patency and end-organ injury, are caused by a more complex composite interaction between systemic and local insults (the main local insult being injury or activation to the vessel wall secondary to perioperative manipulation of the vein graft or because of ischemia/reperfusion).

When considering the many host defense pathways that make up the "systemic inflammatory response," it should be clear that effective taming of the inflammatory response is going to take a multi-targeted pharmacologic intervention. Figure 1 below highlights possible drug targets in the systemic inflammatory response.

SURFACE MODIFICATION—MUCH POTENTIAL BUT LITTLE DELIVERY

The most obvious multi-target intervention is to limit contact activation of fibrinolysis, coagulation, complement, and immune cells by surface modification to make the plastic surfaces of the extracorporeal circuit more biocompatible. Circuit coating thus has the greatest potential to limit the genesis of the "inflammatory response," as opposed to neutralizing effector molecules already generated (1). It must be said that results have been generally disappointing, with the most widespread coating strategy (heparin coating) achieving only modest clinical improvement. The primary target of heparin is thrombin, the most downstream molecule of the intrinsic coagulation cascade.

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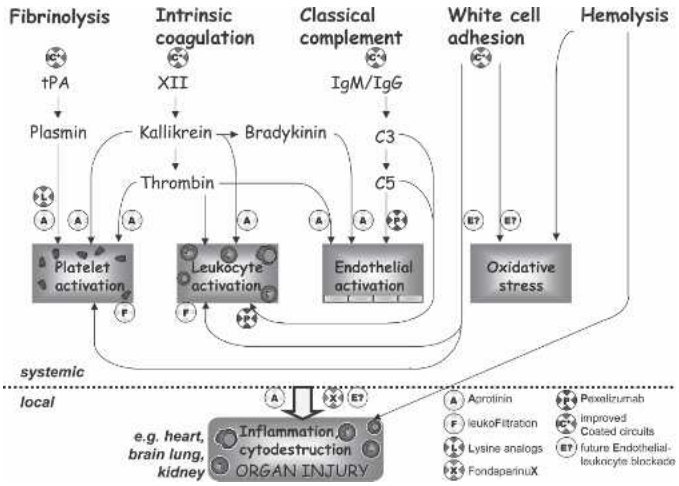

Figure 1. Potential molecular targets in the host response to CPB. Two multi-targeting interventions are shown: aprotinin, a broad acting serine protease inhibitor, and "improved" coated circuits ("improved" because present coating strategies do not efficiently abrogate contact activation). An exciting area for future research is to examine novel pharmacologic agents targeted against the endothelial–leukocyte adhesion cascade; some 30+ such agents, mostly at preclinical–phase II stage, have been developed for use in a host of unrelated inflammatory conditions but may exhibit efficacy in the setting of CPB, possibly in synergy with other mono-targeting drugs such as the complement C5 inhibitor pexelizumab, leukofiltration, or antioxidants.

Ideally, one would want to interdict higher up the cascade, by targeting factor XIIa, IXa, or tissue factor in the extrinsic pathway (2,3). Indeed, whatever beneficial effects heparin coating achieves may be caused by its subsidiary targeting of factor IXa activation of Xa (4). There is some evidence that specifically targeting factor IXa may be highly efficacious (5). A systemic review of circuit coating strategies from an evidence-based perspective concluded that circuit coating merited a disappointing Class II, Level B rating as a means to curb the systemic inflammatory response (6). Clearly, much research remains to be done in order for circuit modification to realize its proper potential as a way to limit contact activation across a broad front in the host response to surgery.

APROTININ: PROMISCUOUS WONDER DRUG OR NEPHROTOXIC MENACE?

As the only FDA-approved compound to limit transfusion requirement in cardiothoracic surgery, aprotinin has been subjected to intensive scrutiny, both for its efficacy and safety. Anti-inflammatory effects have been recognized, which are not seen with other anti-fibrinolytic agents (the lysine analogs tranexamic acid and ε-aminocaproic acid); thus, it is likely that those additional benefits stem from mechanistic actions unrelated to hemostatic targeting of plasmin.

Because aprotinin is a broad-based serine protease inhibitor, it can inhibit a number of potential targets in the host response to surgery (as shown in Figure 1): plasmin, kallikrein, and thrombin receptor protease-activated receptor 1 (PAR1), which is activated by proteolytic cleavage with a serine protease. The actions of aprotinin on the platelet thrombin receptor are discussed in greater detail in a companion article. (7). Although the mechanism of PAR1 targeting is beyond the scope of this article, it is important to remember that thrombin triggers pro-inflammatory pathways in leukocytes and endothelial cells and that aprotinin is therefore likely to mediate anti-inflammatory effects by targeting PAR1 (8). We were able to show this principle in endothelial cells in vitro, in which thrombin-induced calcium fluxes, intracellular signaling, transcription factor upregulation, and interleukin-6 production, were all inhibited by aprotinin (9). A component of aprotinin's anti-inflammatory action is therefore likely to be through PAR1 inhibition on endothelium. Whether aprotinin can exert similar anti-inflammatory effects on leukocytes through PAR1 remains unknown.

Research in the early 1990s showed that aprotinin could inhibit contact activation of platelets and neutrophils in the extracorporeal circuit through targeting of kallikrein (10). Because the inhibition constant (K_i) for kallikrein is much weaker than for plasmin, protection from kallikrein requires a clinical high dose (Hammersmith dose), consisting of 2×10^6 kallikrein inhibitory units (KIUs) in the pump prime, 2×10^6 KIU loading, followed by 0.5×10^6 KIU/h infused intravenously during bypass (11). Animal and in vitro studies have shown that protection from edema and cerebral metabolites leading to stroke was observed at a high dose, through inhibition of bradykinin generation (12). Clinically, a large body of studies support the notion that aprotinin is stroke protective.

Although we still await a prospective randomized clinical trial with stroke as a primary outcome, meta-analyses of studies measuring stroke as a secondary outcome, and studies into neurocognitive impairment, suggest that aprotinin has neuroprotective properties, especially when used at a high dose and in high-risk patients (13–15). A possible mechanism contributing to neuroprotection is by blocking leukocytes from infiltrating into organs (16). This principle was first shown in animal and in vitro work from our group, showing that leukocyte extravasation in response to localized chemotactic stimuli was inhibited by high-dose aprotinin (17,18). Similar findings have since been reported in animal models of ischemia/reperfusion and, most recently, a large animal model of CPB (19,20).

Safety of aprotinin has been the dominant issue in cardiac surgery in 2006/2007. Unfortunately, the highest scientific standards have not always been in evidence during the debate, either by the researchers raising the safety concerns or by the drug's manufacturer, leaving clinicians in a state of limbo. Bayer Pharmaceutical was roundly condemned for withholding safety data from the FDA

hearing into aprotinin in September 2006, and it is hard to know what to make of three observational studies from the Ischemia Research and Education Foundation, which triggered the safety concerns, the first two of which concluded that aprotinin use was linked to renal failure and death (21,22). The third (using the same database as the first two studies) did not find aprotinin as a predictor of renal dysfunction/failure (23).

Prospectively collected safety data from randomized placebo controlled trials has not revealed any increased risk of renal failure leading to dialysis. This includes data from three recent meta-analyses, one of which was an evidence-based review from the Cochrane Collaboration (14,24,25). It should be noted, however, that renal function was not a primary outcome measure in any of the prospective randomized trials carried out to date, and we are thus still working in a certain vacuum of knowledge. A transient rise in serum creatinine levels (not leading to dialysis) has been shown in cardiac surgical patients receiving high-dose aprotinin (25,26). A possible drop in perfusion pressure has been postulated as a theoretical model to explain transient renal dysfunction with aprotinin in patients already receiving angiotensin-converting enzyme (ACE) inhibitors and there is scope for studying this hypothesis in greater depth (27). A good editorial discussing the controversies and safety issues surrounding aprotinin has been published recently in accompaniment to an excellent meta-analysis into the efficacy and safety of the anti-fibrinolytics (25,28). That timely meta-analysis found that none of the anti-fibrinolytics were linked to increased risk of mortality, renal failure, myocardial injury, or stroke in cardiac surgery. Only high-dose aprotinin reduced the risk of re-exploration, but it led to a transient rise in serum creatinine not linked to subsequent dialysis-dependent renal failure. The field is now eagerly awaiting the results of the BART trial (Blood Conservation Using Anti-fibrinolytics: Randomized Trial in High-Risk Cardiac Surgery), the first head-to-head randomized placebo controlled trial into the efficacy and safety of aprotinin, tranexamic acid, and ε-aminocaproic acid. This non–industry-funded trial should have sample sizes large enough to determine adverse drug effects (if any) on rare events such as death from massive hemorrhage, stroke, non-troponin myocardial injuries, and renal failure requiring dialysis—results are expected toward the end of the year.

In light of published and company-held observational datasets, the FDA issued new guidelines in December 2006 recommending that aprotinin use should be limited to patients "who are at an increased risk for blood loss and blood transfusion" in the setting of coronary artery bypass graft surgery with CPB. Furthermore, to address safety concerns regarding hypersensitivity reactions to this bovine protein, the FDA now contraindicates "administration of Trasylol to any patient with a known or suspected prior exposure to Trasylol or other aprotinin-containing products within the previous 12 months." The new FDA guidelines make sense and effectively reinforce existing trends for aprotinin use, which is generally reserved for higher-risk patients, such as those receiving anti-platelet medication (29).

COMBINATIONS OF MONO-TARGETING DRUGS: A WAY FOR THE FUTURE?

Instead of a multi-targeted intervention (such as an improved form of circuit coating or promiscuous protease inhibition), an alternative approach to blocking the many arms of the host response to surgery would be to administer a combination of mono-targeting drugs. This would counter the narrow focus of mono-targeted agents, which have not been able to deliver the anticipated clinical benefits. An example of such a drug is the complement C5 inhibitor Pexelizumab, which despite elegant preclinical research and development work, failed to meet its primary endpoint in phase III clinical trials (30–32). Because Pexelizumab blocks a pathway not specifically targeted by other pharmacologic interventions, it would be interesting to see this compound used in combination with other agents, such as inhibitors of leukocyte diapedesis.

The diapedesis step remains a highly attractive pharmacologic target to limit inflammatory organ injury after CPB. The lack of attention in this area seems puzzling, because it is well established that leukocyte entry and release of cytodestructive mediators represent key stages in organ injury, especially in the context of localized ischemia/reperfusion (16,33,34). A veritable raft of some 30+ novel pharmacologic agents have been developed for blockade of adhesion molecules and chemoattractant receptors involved in the extravasation process; these are at various phases of clinical trial development for treating inflammatory conditions such as inflammatory bowel disease, rheumatoid arthritis, vasculitis, sepsis, atherosclerosis, and more (35,36). It would be most interesting to develop such agents as anti-inflammatory agents for use in surgery with CPB, but to the best of my knowledge, this approach has not yet been attempted. One note of caution when considering using such anti-adhesion molecule therapies is that they have been linked to pro-inflammatory side effects (37,38). Small molecular weight antagonists may avoid the serious side effects of antibody therapies, and it is sobering to consider the failed stroke trial of enlimomab, an anti-intercellular adhesion molecule (ICAM)-1 antibody treatment (39). However, the potential efficacy of targeting the leukocyte-endothelial adhesion pathway has been shown by the "part-time" leukocyte inhibitory effects of the anti-coagulant, fondaparinux. A pentasaccharide motif from fondaparinux not

related to its anti-coagulant properties inhibited leukocyte adhesion and inflammatory injury in a model of kidney ischemia/reperfusion injury (40).

It is disappointing that dedicated agents specifically invented to target the leukocyte transendothelial migration step in other fields have not thus far been tested in the context of cardiothoracic surgery with CPB. Instead, it has been left to part-time inhibitors, such as aprotinin and fondaparinux, to show the principle that such inhibition could exert powerful protection on the systemic inflammatory response.

A useful strategy to complement almost any other form of intervention is leukofiltration (41). Although this does little to prevent inflammatory activation from occurring in the first place, it prevents the most activated (and adhesive) leukocytes and platelets from re-entering the patient circulation.

Further study is also needed into circuit design with a view to curbing the hydrodynamic shear forces exerted on erythrocytes as they pass through the extracorporeal circuit. Hemolysis is an ongoing problem of extracorporeal perfusion, despite being recognized as a concern since the 1970s (42). Recent work has shown that free hemoglobin, once it is released from the protective environment of the red corpuscle, harbors a uniquely bioavailable heme iron moiety that is potently pro-oxidant and is linked to renal failure (43–45). In cardiac surgery, genetic traits associated with impaired scavenging of free hemoglobin are linked to a raft of vascular and perioperative complications in diabetic patients (46–48). An oxidative burst caused by hemolysis occurs at the time of cross-clamp release, contemporaneous with the main burst of microbubble generation, long before systemic cytokines are raised in the circulation (49,50). It is highly likely that modifications to the circuit or cardiotomy suction devices to curb the extent of hemolysis would simultaneously curb microbubble formation (51,52). Antioxidant therapy could also be considered during CPB, especially if used in combination with other anti-inflammatory interventions (53).

CONCLUSIONS

Pharmacologic strategies to curb the systemic inflammatory response to surgery have evolved in large part from existing agents used to control bleeding and coagulation (e.g., aprotinin and heparin coating of circuits). Very few dedicated anti-inflammatory agents have been developed specifically to combat the inflammatory response and, where they have, their therapeutic target may have been too narrow to blunt the multi-system etiology of the systemic inflammatory response. An inescapable truth would seem to be that a multi-system disorder such as the host response to CPB requires a multi-targeted intervention, either through the use multi-targeting intervention (e.g., serine protease inhibition or improved circuit coating) or a combination of mono-targeting interventions (e.g., anti-fibrinolytic, anti-coagulant, anti-complement, anti-leukocyte, anti-cytokine, and antioxidant treatments). Safety issues related to the use of anti-fibrinolytics in cardiac surgery dictate that clinical trials in future be adequately powered to detect clearly defined adverse events, such as stroke, myocardial injury, and acute renal failure requiring dialysis.

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Pharmacologic Neuroprotection: The Search Continues

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Abstract: Dozens of drugs have been studied in an attempt to mitigate the adverse cerebral consequences of cardiac surgery. The targets for these drugs have focused on pathways identified through the cascade of events that occurs once cerebral ischemia is initiated. In addition, inflammatory targets specific to cardiopulmonary bypass have also been addressed. Although no drugs are yet approved as specific neuroprotective agents, trials continue of increasingly unique targets, with fewer unwanted side effects and acting through novel mechanisms of action. This review summarizes the past, present, and future of pharmacologic neuroprotection for cardiac surgery. **Keywords:** cardiac surgery, cardiopulmonary bypass, brain, neuroprotection, pharmacology. *JECT. 2007;39:296–301*

INTRODUCTION

Cerebral complications continue to be a well-recognized source of morbidity and mortality after cardiac surgery (1). Although the early decades of cardiac surgery were largely focused on improving myocardial outcome and its effect on overall patient survival, neurologic injury was clearly recognized. The study of cardiac surgery–related cerebral injury has since followed a logical time-course establishing a stepwise path toward the goal of neuroprotection. Initial descriptive studies focused on the incidence of, and risk factors for, perioperative neurologic injury. In addition to studies of the cerebral physiologic effects of cardiopulmonary bypass (CPB), multiple technologic advancements in the CPB apparatus were also identified, thus forming the early basis for non-pharmacologic methods to prevent neurologic injury. Early efforts to identify pharmacologic neuroprotectants (e.g., barbiturates) developed based on the understanding of the apparent importance of metabolic suppression to protect the ischemic neuron. In addition to the improvements in CPB technology, knowledge of the molecular workings of the brain has improved significantly, revealing potential pharmacologic neuroprotective targets.

The understanding of the pathophysiology of cerebral injury continues to evolve. The oversimplified concept that depletion of high energy phosphates and the destruction of brain tissue that rapidly follows ischemia has largely been replaced with more complex temporal, topographic, and biochemical considerations. Imaging techniques have elaborated on the spatial gradations of residual blood flow in the downstream territory of an occluded cerebral vessel. This ischemic "penumbra," where blood flow is critically reduced but still sufficient to prevent immediate cell death, has formed the basis for drug therapy targeted to rescue this vulnerable yet salvageable tissue. There is a marked difference in the temporal association between the ischemic insult and eventual cell death, thus defining the "therapeutic window" during which intervention may attenuate infarct size.

An ischemic cascade is triggered by reductions in cerebral blood flow (CBF), either globally or regionally, when the demands of cerebral metabolism ($CMRO_2$) are no longer met (2). This depletion in cerebral energy stores leads to membrane ionic pump failure and a consequent series of injurious events mediated through the influx of sodium, the opening of voltage-dependent calcium gates, a release of stored intracellular calcium, and overall membrane depolarization. Membrane depolarization results in the release of excitatory amino acids (glutamate, aspartate) with subsequent dramatic increases in intracellular calcium. This increase in cytoplasmic calcium propagates the cascade through the activation of a number of calcium-dependent enzymes, including endonucleases, nitric oxide synthase, various proteases, protein kinases, and phospholipase. Without intervention, these enzymes eventually lead to neuronal death.

Although some of these ischemic cascade pathways are potentially reversible if reperfusion is quickly re-established, reperfusion itself may initiate a number of other destructive pathways. The re-establishment of oxy-

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gen delivery provides substrate for the production of free radicals. Reperfusion can initiate a number of other damaging extracellular events including blood–brain barrier breakdown, endothelial swelling, and localized thrombosis that together may culminate in microvascular occlusion and further ischemia. Each ischemic cascade pathway represents a specific target for neuroprotection and has formed the basis for the initiation of pharmacologic neuroprotective strategies, both in non-surgical, as well as cardiac surgery, settings.

There are currently no pharmacologic therapies approved by the regulatory agencies for the prevention or treatment of cardiac surgery–associated cerebral injury. Numerous studies of specific pharmacologic agents have been undertaken in cardiac surgery studies, and it continues to be an active area of research. The most relevant cardiac surgery pharmacologic neuroprotection strategies, past and present, will be reviewed below. In addition, future trials, either being planned or underway, will also be reviewed.

PHARMACOLOGIC NEUROPROTECTIVE DRUGS

Anesthetic agents have long been thought to process neuroprotective properties and were among the first compounds studied for neuroprotection in cardiac surgery. Indeed, the barbiturate, thiopental, was one of the first agents studied for this purpose during cardiac surgery. In a study by Nussmeier et al. (3), thiopental was administered (until EEG burst suppression) before aortic cannulation and continued until separation from CPB. Postoperative neurologic complications on postoperative day 10 were significantly reduced in the thiopental group vs. controls. Based on the encouraging results of this trial, high-dose thiopental was frequently used for valvular and other open ventricular procedures. The proposed mechanism for this neuroprotective effect related to the salutary effects of barbiturates on cerebral metabolism. This mechanism, along with considerable experimental data reporting the beneficial effects of the barbiturates (4), made it a logical choice for cardiac surgery. However, further studies of the use of thiopental were not quite as positive. A study by Pascoe et al. (5) and one by Zaidan et al. (6) failed to support a beneficial effect of thiopental on neurologic outcome after cardiac surgery. These negative trials coupled with the side effects of prolonged sedation tempered the optimism for barbiturates. Retrospectively examining the initial study of Nussmeier et al., the beneficial effects of thiopental, although not shown in longer-term follow-up, may not have been related to a direct neuroprotective effect per se, but because of an indirect effect on reducing emboli-containing CBF. The well-known cerebral vasoconstricting effects of thiopental (coupling CBF with a barbiturate-induced reduction in $CMRO_2$) may have resulted in a reduction in embolic load to the brain during CPB, and as a result, a beneficial effect on neurologic outcome. Furthermore, it has subsequently been experimentally shown that isoelectricity per se is not necessary to confer neuroprotective benefit from barbiturates (7). The evaluation of burst suppressive doses of thiopental have not been performed in this setting.

Propofol has similar effects on $CMRO_2$ and CBF as thiopental. In addition, it has also been shown to possess some antioxidant and calcium-channel antagonist properties (8). This, along with supportive data from the experimental cerebral ischemia studies (9–11), led to propofol being evaluated as a neuroprotectant during cardiac surgery. A prospective randomized clinical trial by Roach et al. (12) determined whether propofol-induced EEG burst suppression would reduce the incidence or severity of cerebral injury during valvular surgery. However, in 109 of 215 patients randomized to receive burst-suppressive doses of propofol, there was no beneficial effect on cognitive outcome at 2 months. These authors concluded that propofol provided no neuroprotection during valvular cardiac surgery. One caveat is that studies in non-valve cardiac surgery have not assessed the effects of propofol on the brain, but one can speculate that the results would be no different.

Clomethiazole, an antagonist at the γ-aminobutyric acid (GABA) receptor, has recently been evaluated in coronary artery bypass grafting (CABG) surgery. The rationale to this study was that GABA has repeatedly been shown to be an important neuroprotective target in focal and global experimental ischemia (13,14). However, in a relatively large well-designed and conducted study, it failed to have any effect on preventing neurocognitive dysfunction after cardiac surgery (15).

The adenosine-regulating agent, acadesine, was studied in the early 1990s with the expressed purpose of improving myocardial outcome. However, evaluations for stroke (as a secondary outcome) were also performed (16). Compared to placebo, both high- and low-dose infusions of acadesine resulted in a lower stroke rate ($p = 0.016$) (17,18). Despite this positive (albeit indirect) clinical data and supportive experimental data, no further clinical neuroprotection indication for acadesine has been pursued (19). There are a number of other adenosine-like agents that in pre-clinical experimental settings have provided neuroprotection.

Aprotinin is a non-specific serine protease inhibitor that was first used for the treatment of pancreatitis. Its current indication in cardiac surgery is for the prevention of blood loss and transfusion. In several large multi-center trials of aprotinin for primary or redo CABG and valvular surgery designed to evaluate its blood loss and transfusion reducing effects, high-dose aprotinin patients suffered fewer strokes compared with placebo patients ($p = .032$)

(20,21). In a similar fashion, Frumento et al. (22) retrospectively examined patients at high risk for stroke (because of the presence of significant aortic atheroma); those who received aprotinin had a significantly lower stroke rate. In a recent small ($n = 36$) study examining the effects of aprotinin on cognitive deficits after CABG surgery, the incidence of cognitive loss was reduced in the aprotinin group (58% aprotinin vs. 94% placebo; $p = .01$) (23). However, the high incidence in the placebo group, coupled with the small size of the study and other methodologic concerns, limits the applicability of these results to broader populations (24). Furthermore, animal studies in cerebral ischemia models have failed to show any direct benefit on either functional or neurohistologic outcome after cerebral ischemia (25).

There has been considerable discussion and study as to the potential mechanism for any aprotinin-derived neuroprotection. Initial enthusiasm focused on its anti-inflammatory effects potentially preventing some of the adverse inflammatory sequelae of cerebral ischemia. However, any direct neuroprotective effect may have been mediated through an indirect effect in modulating cerebral emboli. Brooker et al. (26) identified the cardiotomy suction of mediastinal shed blood as a major source of cerebral emboli during CPB. One could extrapolate that, if a drug reduces the amount of particulate-containing blood returning from the operative field to the cardiotomy reservoir (by decreasing overall blood loss), cerebral emboli (and the resulting neurologic consequences) might also be decreased.

More recently, additional doubt as to any direct neuroprotective effects of aprotinin has been tabled in a controversial publication by Mangano et al. (27). Contrary to the previous data that suggested, albeit very weakly, that aprotinin may have some neuroprotective effects, this particular study outlined a significant increase (181%) in the stroke rate after cardiac surgery. Although the observational nature of this study and the propensity analysis used to control for the high risk of the patients receiving aprotinin did not delve into the mechanism for this potential side effect, it has been suggested that any potential neurologic risk is likely related to prothrombotic effects. However, the multiple modes of action of this non-specific serine protease inhibitor make it difficult to confidently explain these results based on one solitary mechanism. In summary, the data suggesting that aprotinin had any neuroprotection were somewhat indirect and weak; however, the data suggesting that it is neurologically detrimental are similarly just as weak. The true effects of aprotinin on the brain remain incompletely understood and would benefit greatly from prospective study.

The influence of calcium plays a central role in propagating cerebral ischemic injury. For this reason, as well as a shown beneficial effect of the calcium channel blocker nimodipine in subarachnoid hemorrhage and experimental cerebral ischemia, a randomized double-blind placebo, single center trial to access the effect on nimodipine on neurologic, neuro-opthalmologic, and neuropsychologic outcomes after valvular surgery was performed (28–30). However, the trial was stopped before completion of enrollment because of safety concerns related to an increased bleeding and death rate in the nimodipine group. In addition, there was also no difference in neuropsychologic deficits between the placebo or nimodipine groups at this interim review. As a result, the effect of this drug, or similar calcium trial blockers, will likely never be fully elucidated in CPB.

The monosialoganglioside, GM1-ganglioside, has also been studied as a potential neuroprotectant during cardiac surgery (31). In addition to the potential beneficial effects of this class of compound on preserving neuronal membranes, there are also some data to suggest that it has a potential beneficial effect on reducing excitatory amino acid transmission (32). In a preliminary (but underpowered) cardiac surgery study, no beneficial effect was shown. This trial highlights one of the biggest difficulties in this investigative field—the interpretation of negative but underpowered studies.

The *N*-methyl-D-aspartate (NMDA) receptor is known to play a central role in the ischemic cascade (2). Although human stroke trials have been limited by variable psychomimetic side effects, there is considerable experimental data identifying NMDA receptor antagonists as robust neuroprotective agents. It has also been postulated to play a potential role in CPB-associated cerebral injury (33). In a well-designed and executed study by Arrowsmith et al. (33), the effects of remacemide, given orally for 4 days before CABG, was assessed by administering a neurocognitive battery performed at 1 week before and 8 weeks after CABG. A deficit was defined as a decrease in 1 SD in 2 or more of the 12 tests within the neurocognitive battery. In addition, the patients were evaluated for their learning ability by subtracting the postoperative neurocognitive score from the preoperative score (thus formulating a Z score). Although there was no difference between groups with respect to the binary outcome of cognitive deficit ($p = .6$), examination of a continuous measure of learning ability showed a beneficial cognitive effect in the remacemide patients ($p = .028$). Despite these apparently beneficial results, this drug was never pursued for this indication. This was in part because of the length of time that it took to perform this single center trial, the initial non-beneficial preliminary results, and a prolonged period of data analysis and review for publication. It did, however, highlight the potential use of this class of drugs for this indication and, as a result, ongoing studies examining other NMDA receptor antagonists continue (34–36).

A second NMDA receptor antagonist that has been evaluated for neuroprotection during cardiac surgery is dextromethorphan. Dextromethorphan, known for its anti-tussive activity, has been shown to have some non-specific NMDA antagonism properties. A small ($n = 12$) pilot study in pediatric cardiac surgery examined dextromethorphan using both EEG and magnetic resonance imaging endpoints to determine a difference between treatment groups. However, no difference was found, most likely because of the small size of the study (37). There have been no other studies examining NMDA receptor antagonism in the setting of pediatric cardiac surgery.

Ketamine, a frequently used anesthetic that is also an NMDA receptor antagonist, was evaluated for its neuroprotective effects in a small ($n = 106$) study in cardiac surgery patients (38). The incidence of neurocognitive dysfunction 10 weeks after surgery trended toward being lower in the ketamine group (20% ketamine vs. 25% controls; $p = .54$), but because the study was underpowered, it was not a significant change. There are no other published trials evaluating ketamine for neuroprotection in this setting.

Lidocaine has both properties as a sodium channel-blocking agent and potential anti-inflammatory effects. It has been studied as a neuroprotectant in cardiac surgery in several studies. In a study of 55 patients undergoing valvular surgery, a lidocaine infusion (1 mg/min) was started pre-induction and maintained for 48 hours after CABG surgery (39). Neurocognitive testing was performed preoperatively and then 8 days and 2 and 6 months postoperatively. Compared with placebo, neurocognitive outcome 8 days after the surgery was significantly better in the lidocaine group ($p = .025$). However, a much larger, and more definitive, double blind randomized trial in cardiac surgery failed to replicate the finding. Interestingly, not only did lidocaine not confer any benefit, but in diabetic patients, it actually worsened neurocognitive outcome. Currently, lidocaine cannot be recommended as a clinical neuroprotective agent in cardiac surgery (40).

β-blocker use in patients with cardiac disease has predominately been directed towards the prevention of adverse myocardial events. However, in a retrospective study ($n = \sim3000$) of neurologic outcomes after cardiac surgery, β-blocker use was associated with an improvement in composite neurologic outcome (stroke and encephalopathy) (41). Patients receiving β-blocker therapy had a significantly lower incidence of neurologic deficit vs. those not receiving β-blockers. Although the reasons for this potential benefit were not clear, there are several potential reasons why they may be efficacious. For example, β-blockers have been shown to modulate both cerebrovascular tone and CPB-related inflammatory events. Support for the potential neuroprotective effects from β-blockers has similarly been shown in a study of carvedilol, a mixed adrenergic antagonist effect also possessing anti-oxidant and anti-apoptotic effects (42).

Reactive oxygen species (ROS) production is a well-described pathophysiologic mechanism of ischemic reperfusion injury. When combined with the whole body inflammatory response associated with CPB (and its own associated generation of ROS), the field of antioxidant therapies for neuroprotection after cardiac surgery has emerged. Superoxide dismutase (SOD) is involved in the catabolism of free radicals, and SOD mimetics have had beneficial results in the setting of experimental ischemia. Pegorgotein, a monomethyoxypolyethyleneglycol covalently linked to SOD, has experimentally been shown to be protective against reperfusion-mediated cardiac and neuronal injury (43). A clinical trial was carried out to examine whether it would be associated with a reduced number of neurocognitive deficits after cardiac surgery (44). However, in a study of 67 patients undergoing CABG surgery ($n = 22$–23 in each of three groups: placebo, 200 IU/kg pegorgotein, or 5000 IU/kg pegorgotein), no difference in neurocognitive outcome was found.

Complement activation is central to the inflammatory response initiated with CPB (45). In a small ($n = 18$) study using a simple assessment of cognitive function, patients receiving an inhibitor to C5 (h5G1.1-scFv; pexelizumab) showed fewer visuospatial deficits at hospital discharge (46). Additional large (phase III) trials of this compound to more adequately delineate any potential longer-term neuroprotective effects from this drug in this setting have been performed. Mathew et al. (46) studied pexelizumab in a 914 patient study aimed at evaluating its effect on both myocardial outcome and mortality. The secondary endpoint of neurocognitive outcome showed that pexelizumab, although having no effect on overall global measures of cognitive outcome, seemed to have a specific benefit on the visuospatial domain.

Platelet activating factor (PAF) antagonists have been shown to have neuroprotective effects in various experimental models of cerebral ischemia (47). PAF modulates post-ischemic injury through the release of cerebral cellular lipids and free fatty acids that consequently lead to cellular injury and cerebral edema (48). In a study of 150 cardiac surgery patients by Taggart (49), patients receiving either placebo or one of two different doses of Lexiphant showed no protective effects on neurocognitive outcome 3 months after cardiac surgery. However, this study was again underpowered, which is a recurring and troublesome feature of many studies in this area.

Because of their ability to reduce the inflammatory response, corticosteroids have long been considered as potential cerebroprotective agents. Inflammation is considered an important factor in propagating ischemia-mediated brain injury (50,51). With the exception of spinal

cord injury (52), steroids have never been shown to possess any significant clinical neuroprotective properties. Indeed, in a prior CABG trial, they actually had an adverse effect on postoperative pulmonary function (53). Furthermore, the administration of steroids has been shown to worsen cerebral outcome in a recent large (n = 10,000), although non-cardiac, surgical trial. The CRASH trial showed an increased relative risk of death (1.18; 95% confidence interval, 1.09–1.27; p = .0001) in those receiving high-dose steroids within 8 hours of head injury (54,55). Part of their lack of effect may be because of the hyperglycemia that generally follows their administration. Hyperglycemia, in animal models and several human studies of cerebral injury, has been associated with worsened neurologic outcome (56,57). Hyperglycemia has also been shown to increase the incidence of cognitive deficits after CPB (58). The administration of steroids with the intent of conferring some degree of neuroprotection during cardiac surgery cannot be recommended.

FUTURE NEUROPROTECTIVE DRUG TRIALS

There are several drugs undergoing active study as neuroprotective agents in the setting of cardiac surgery. Most of these drugs use neurocognitive dysfunction, or mild cognitive impairment, as a primary endpoint.

Dexanabinol is one such potential neuroprotective compound that is a synthetic non-competitive NMDA receptor antagonist. It also possesses some tumor necrosis factor (TNF)-α antagonist properties. It's neuroprotective potential has been evaluated extensively experimentally in the setting of various models of cerebral ischemia (59,60). It is currently being evaluated in early phase clinical trials in CABG for the prevention of neurocognitive dysfunction. In addition to the dexanabinol trial, other peptides are also under study. One of these, AL-208 is an eight amino acid activity-dependent neurotrophic factor that is secreted by allele cells in response to stimulation by vasoactive intestinal protein. In addition to anti-apoptotic activity, it has also been shown to promote neurite outgrowth and stabilize microtubules. It is currently underway in a phase II trial in CABG surgery.

Another growth factor–related peptide, glypromate (glycine-proline-glutamate), is an insulin-like growth factor 1 and has completed a small phase II trial (n = 30). Furthermore, a small phase I CABG trial (n = 20) was undertaken of the energy substrate–providing ketone body drug, KTX-0101 (sodium α-hydroxybutyrate), but the results have not been reported. Several other proprietary compounds are also undergoing evaluation and have yet to be reported.

In summary, despite decades of work, and the studies of dozens of drugs, the prospect of having a robust pharmacologic neuroprotective agent does not yet seem promising. However, with a better understanding of the etiology and mechanisms of neurologic injury, studies will continue to be undertaken. Clearly, when it comes to neuroprotection, the search continues, but the answers have thus far remained elusive.

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Twenty Years Trying to Protect the Brain: What Do We Know?

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Abstract: Thirty-five years ago at the Nixon Watergate hearings, a young attorney named Fred Thompson, current US presidential candidate, asked "What did the President know and when did he know it?" A couple of word changes and this question would be appropriate to ask any number of surgical specialties regarding negative neurologic outcomes. Even today, some specialties are in denial about impaired brain function after surgical intervention. Fortunately, the cardiac surgery community has been in the forefront in efforts to protect the brain. **Keywords:** cardiopulmonary bypass, brain injury, cardiac surgery, neurological protection. *JECT. 2007;39:302–304*

INTRODUCTION

The year 1973 (my first year in Houston where I became interested in neurologic outcomes after cardiac surgery) was a time when not dying after heart surgery was considered a very successful operation, and any organ disruption, other than the heart, was accepted as unavoidable. During the next decade, the death rate and overt stroke numbers plummeted as improvements in technology, especially cardiopulmonary bypass (CPB) apparatus, and associated improvements in techniques resulted in improved outcomes.

As better monitoring tools have become available over the past two decades, the etiologic factors associated with brain injury have been identified, and new methods and apparatus have been adopted into practice. Changes in temperature, blood management, new anesthetic and blood gases regimens, different clamps, improved cell savers, ultrasonic aortic evaluations, and changes in CPB technology have resulted in a dramatic improvement in patient outcomes, not only for the brain, but for all organs, despite patients being older and sicker.

The etiologic factors affecting neurologic outcome after CPB are largely known after 20 years of diligent detective work. Armed with new insights regarding how brain function can be impaired during and after surgical intervention, most of the deleterious effects can be avoided by an alert and motivated cardiac surgical team.

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ACUTE SYMPTOMS OF BRAIN INJURY

The first premise is that disrupted brain function may be transient and related to alterations and imbalances in blood chemistry. As equilibrium is restored, so is normal brain function. One must be careful to discriminate between brain lesions and brain impairment. Delirium is characterized by an acute change in cognition and a disturbance of consciousness often associated with a high fever and a generalized systemic inflammatory response syndrome (SIRS).

At Wake Forest University Baptist Medical Center, the low incidence of postoperative delirium seen in coronary artery bypass grafting (CABG) patients has been achieved because of the introduction of the following practices.

1. Keeping our arterial inflow temperatures < 37.5 C, thereby not assaulting the brain structures in the anterior thalamus and hypophysis (pituitary), which control temperature and monitor insulin production, with a hyperthermic insult. It takes between 1 and 2 seconds for blood to travel from the arterial filter to the Circle of Willis, so the temperature of the blood, as it leaves the CPB circuit, is approximately the same as when it perfuses the temperature-regulating system of the brain. It is also not a surprise that blood glucose and insulin levels are in a dynamic state after the pituitary experiences a hyperthermic shock. Consciousness is also affected by rapid changes in both blood sugar and insulin (as in insulin shock), and these same structures are also important in blood chemistry monitoring.
2. Minimizing SIRS is critical for avoiding postoperative

delirium. We believe that careful blood management, which is best described as preventing blood loss through careful surgical technique and the use of aprotinin, is associated with a decrease in patient temperature fluctuations in the intensive care unit (ICU) and more rapid recovery of a normal sensorium. Minimizing transfusion products is controversial, but there is no question that increased blood product use is correlated with worse outcomes (1). Aprotinin seems to protect the integrity of the endothelium and prevents "leaking," which causes edema. Having a swollen brain (blood–brain barrier breakdown) is not conducive to clear thinking (2,3).

3. Reducing deformable embolic load during CPB. By minimizing blood loss, cardiotomy suction return can be avoided, which is a major source of lipid and gaseous microemboli (MEs) (4,5). The passage of MEs through the cerebrovasculature results in endothelial disruption, brain edema, and cell stress.

CHRONIC OR LONG TERM BRAIN INJURY

A focal ischemic lesion, an infarct, will cause symptoms within minutes, although the dysfunction may be "silent" to the neurologically unsophisticated and even the patient. Typically it takes about 6 months before the damaged area stabilizes, the edema dissipates, and an assessment of the permanent disability can be estimated. By then, ~90% of the improvement of the initial injury has been realized, and after a year, there is generally no further improvement.

Conversely, the damage caused by microemboli, inflammation, and edema may take quite some time to develop, and the loss of cell mass may not be obvious until several months have passed (3). Assessment of function at this delayed period is problematic because the patient's ongoing vascular disease is contributing to a potential decline in function as well.

If the cardiac team desires to use alterations in brain function to modify their surgical techniques, the best definition of a perioperative brain-related disorder is one that is consistent at 1 week, 1 month, and 6 months (6).

We have recently evaluated our data using this definition and have shown that the number of patients who develop neurologic symptoms 1 month or longer after surgery can be predicted based on age, and this occurs at the same predicted rate that neurologic events would occur in an unoperated population (7). Using the definition of a "persistent" deficit, we find striking differences in patients who had only a single cross-clamp applied (9%) compared with patients who had multiple applications of clamps (26%) (6).

Our experience obtained over 20 years of NIH-funded research on the topic of brain protection during cardiac surgery can be categorized into three areas.

1. Blood management
   i. Minimizing bleeding by taking extra care going in "dry."
   ii. Using aprotinin in a large percentage of the patients where appropriate. Treating suctioned blood from the thoracic surgical field through a continuous autologous cell saver, when possible (5,8).
   iii. Avoiding suction blood, minimizing the introduction of deformable lipid and gaseous MEs that may initiate SIRS, occlude vessels, and cause brain swelling.
2. Temperature control
   i. Never exceeding 37.5°C with the arterial inflow blood and care with the addition of any perfusates (because perfusates much cooler than blood temperature may afford the significant possibility of out gassing of gaseous MEs).
   ii. An embolic occlusion resulting in an infarct at temperatures in excess of 37.5°C will result in a lesion with a 10-fold greater volume than if the occlusion was initiated at 32°C.
3. Aortic manipulation
   i. The use of a single cross-clamp method, placed after epi-aortic evaluation of the aorta.
   ii. Avoiding partial occlusion and using a "soft," springy jawed clamp. Hard clamps disrupt the lining of aorta, resulting in a source of continued embolization from clots and necrotic debris in the days immediately after surgery (9).

The surgical team at Wake Forest University Baptist Medical Center, led by Dr John Hammon, have achieved a fivefold improvement in 6-month neurologic outcome over the past two decades by systematically integrating the insights obtained from the research of the CardioNeuroProtection team. The relationship and interaction between the basic scientists, histologists, radiologist, anesthesiologist, engineer, nurses, and perfusionists have allowed us to make a safe operation even safer.

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Why Thrombin PAR1 Receptors Are Important to the Cardiac Surgical Patient

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Abstract: Targeting of the high-affinity thrombin receptor protease-activated receptor-1 (PAR1) on platelets represents an exciting strategy to curb the pro-thrombotic complications of cardiac surgery without interfering with the hemostatic benefits of thrombin in the coagulation cascade. The first dedicated PAR1 antagonist to complete safety trials this year has justified expectations, showing no increased risk of bleeding when added to standard anti-platelet therapy but halving major adverse cardiovascular events after percutaneous coronary intervention. In the setting of cardiothoracic surgery with cardiopulmonary bypass, an FDA-approved drug already exists with anti-PAR1 properties: aprotinin has been shown to inhibit thrombin-induced platelet activation in vitro and clinically, through sparing of PAR1 receptor cleavage and activation. Because aprotinin also exerts anti-fibrinolytic effects through blockade of plasmin, this indicates a subtle clinical mechanism of action that is simultaneously anti-thrombotic yet hemostatic. PAR1 antagonists would also be expected to exert anti-inflammatory properties through targeting of PAR1 on endothelium, and this principle has been validated in vitro for aprotinin and newer peptidomimetric antagonists. PAR1 antagonism is likely to remain an active and exciting area of research in cardiac surgery, with newer generations of PAR1 antagonists and recombinant aprotinin variants entering clinical development. **Keywords:** cardiac surgery, thrombin, receptor, antagonist. *JECT. 2007;39:305–307*

PAR RECEPTORS: SENSORS OF INJURY

Protease-activated receptors (PARs) use a weird and wonderful ligand receptor activation mechanism that allows them to sense changes in the proteolytic milieu. Whereas other receptors recognize ligands carried in solution phase, the PARs receptors carry their ligand (a hexapeptide motif) within their own receptor exodomain. The hexapeptide ligand, however, remains inaccessible to the receptor binding pocket until unveiled by cleavage with a serine protease (1). The newly created N terminus (with the hexapeptide now at the end) folds back into the body of the receptor and docks within the binding pocket (2). From then on, downstream signaling through G proteins and cell activation is similar to other G protein–coupled receptors of the same seven-transmembrane superfamily.

This unique activation mechanism allows PARs to sense the presence of serine proteases in the environment, not just thrombin. Because PARs receptors are found on all cells of the vasculature and the vessel wall, they provide a critical sensing mechanism allowing the body to respond to surgery and cardiopulmonary bypass (CPB; which is known to activate a range of critical serine proteases, including thrombin, kallikrein, plasmin, tryptase, elastase, and others) (3). Three of the four PAR receptors (PAR1, -3, and -4) are cleaved by the serine protease activity of thrombin and can therefore be considered thrombin receptors (4). PAR1 is the high affinity thrombin receptor and PAR4 is the low affinity thrombin receptor on platelets. PAR3 is poorly understood but may be an important thrombin receptor on vascular cells. PAR2 is the odd one out, because it is not a thrombin receptor, being cleaved instead by trypsin, mast cell tryptase, or the ternary coagulation complex of factor Xa-VIIa-TF.

Although PAR1 is recognized for being the high-affinity thrombin receptor, and thus of critical importance to platelet involvement in thrombosis, it should be remembered that other serine proteases, notably trypsin, kallikrein, and low concentrations of plasmin, can also cleave and activate PAR1 (3,5). This is important when considering the effect of serine protease inhibitors in cardiac surgery.

The reason there is so much excitement about the use of thrombin receptor antagonists in cardiac surgery is that they promise to abrogate the pro-thrombotic actions of thrombin on platelets while leaving the coagulation cascade largely untouched—the hope is that thrombotic

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events can be eliminated without causing undue risk of bleeding (6).

PROMISE OF TARGETING PAR1 IN CARDIAC SURGERY

Several PAR1 antagonists are in clinical development. The most advanced, which just completed glowing safety trials for use in percutaneous coronary intervention (PCI) and is now in a 10,000 patient phase III trial, is a peptide antagonist based on the hexapeptide ligand sequence (7). This blocking peptide sits in the ligand binding pocket and prevents access to the natural ligand, even when that is generated after proteolytic cleavage of PAR1 with thrombin (8). The phase II TRA-PCI safety trial met its primary safety endpoint, showing no increase in thrombolysis in myocardial infarction (TIMI) bleeding when added to standard anti-platelet care, but showing a 46% reduction in major adverse clinical events (7). Figure 1 shows how PAR1 antagonists can block thrombotic complications by preventing platelet activation caused by thrombin, whereas they do not interfere with the hemostatic properties of thrombin in the coagulation cascade.

Although specific PAR1 antagonists have stolen the limelight in 2007, the first clinical demonstration of PAR1 antagonism came in 2004 through the use of aprotinin in cardiothoracic surgery with CPB.

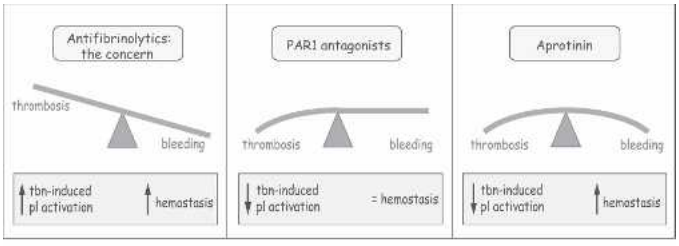
PAR1 TARGETING BY APROTININ: TEACHING AN OLD DOG NEW TRICKS

Aprotinin is a broad-spectrum serine protease inhibitor first isolated from cow lung in 1936. It was shown to be a plasmin inhibitor in 1979, and its clinical anti-fibrinolytic properties were co-discovered in 1987 by groups in the United Kingdom and Holland (9,10). From the first studies in cardiothoracic surgery, aprotinin was recognized to preserve platelet function (10). Elegant electron microscopy studies showed that platelet morphology was completely preserved throughout CPB (11). The critical study into the mechanism of platelet protection came in 1998 from a study by Victor Ferraris, which showed excessive bleeding was linked to activation and degranulation of platelets through the high-affinity thrombin receptor PAR1 (12).

Given that thrombin activates PAR1 through a serine protease mechanism and that aprotinin is a serine protease inhibitor, we hypothesized that aprotinin should possess anti-thrombotic properties by preventing thrombin-induced platelet activation. This hypothesis was controversial at the time, following the ambiguous results of the IMAGE trial into graft patency (13). We first studied the effect of aprotinin on washed human platelets and were able to show a dose-dependent inhibition of thrombin-induced platelet aggregation (14). This was achieved at clinically relevant concentrations of aprotinin: 42.6 ± 21.6% inhibition at 50 KIU/mL ($p = .0047$), 61.0 ± 25.2% inhibition at 100 KIU/mL ($p = .0001$), and 86.6 ± 8.9% inhibition at 160 KIU/mL ($p < .0001$).

We next examined whether aprotinin could inhibit PAR1 activation clinically (15). This study confirmed that (i) thrombin was generated during passage of blood through the bypass circuit; (ii) platelets were activated by thrombin because of cleavage of PAR1; (iii) high-dose (Hammersmith dose) aprotinin prevented platelet activation through PAR1 without affecting net thrombin generation; and (iv) the mechanism of PAR1 protection was by preventing proteolytic cleavage of PAR1. In vitro, the mechanism is definitively through targeting of thrombin-induced PAR1 activation. Clinically, we cannot rule out the possibility that aprotinin may also target plasmin and kallikrein, both of which can cleave and activate PAR1, in addition to thrombin.

This clinical study therefore revealed a subtle "anti-thrombotic yet hemostatic mechanism" of action for aprotinin when used in cardiothoracic surgery (Figure 1): anti-thrombotic by virtue of preventing thrombin-induced platelet activation and hemostatic by virtue of anti-fibrinolytic targeting of plasmin. Thus, like the more modern peptidomimetric PAR1 antagonists, this opportunistic PAR1 antagonist is able to exert anti-thrombotic properties without increasing the risk of bleeding. Better still, because of its additional targeting of plasmin in the fibrinolytic pathway, aprotinin simultaneously delivers anti-thrombotic and hemostatic properties. This is an exceptionally useful pharmacologic profile for a compound used primarily as a hemostatic agent in cardiothoracic surgery.



Abbreviations: PAR1 = protease activated receptor 1, tbn = thrombin

Figure 1. Anti-fibrinolytics and PAR1 antagonists in cardiac surgery. (Left) A concern in cardiothoracic surgery is that, although anti-fibrinolytics are effective at reducing bleeding, might they not also present a concomitant risk of thrombosis? (Middle) The promise of PAR1 antagonists is that they can inhibit the action of thrombin on platelets while maintaining the hemostatic properties of thrombin in the coagulation cascade. (Right) The TRA-PCI study (phase II safety trial) seems to have borne out this early promise by noting no increase in TIMI bleeding but a 46% reduction in major adverse cardiovascular events after percutaneous coronary intervention. Aprotinin exhibits anti-thrombotic properties in on- and off-pump surgery by inhibiting thrombin-induced platelet activation through PAR1, yet it exhibits simultaneous hemostatic properties by blocking plasmin in the fibrinolytic pathway. tbn, thrombin.

Similar anti-thrombotic yet hemostatic properties of aprotinin have been observed in animal models of thrombosis and clinically in off-pump surgery (16,17). Meta-analyses of the randomized trials have borne out that aprotinin does not add risk to graft patency but significantly lowers the risk of stroke (18). A possible mechanism contributing to stroke protection is through reduced perioperative platelet activation by thrombin (19). Another contributory mechanism would be through reduced thrombin activation of endothelium, which is expected to yield anti-inflammatory and anti-thrombotic drug effects (20).

CONCLUSIONS

Clinical phase II trials in 2007 seem to have borne out anticipated anti-thrombotic benefits of PAR1 antagonism not linked to an increased risk of bleeding. The first clinical demonstration of PAR1 antagonism, however, came from earlier work using the anti-fibrinolytic agent aprotinin. This possesses PAR1 antagonistic properties by virtue of blocking proteolytic activation of PAR1 by thrombin. It is anticipated that PAR1 antagonism will remain an active field for further development in cardiothoracic surgery with CPB, because it holds the prospect of reducing thrombotic complications without incurring a concomitant bleeding risk or even while realizing a simultaneous anti-fibrinolytic hemostatic benefit.

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Antifibrinolytic Therapy: Evidence, Bias, Confounding (and Politics!)

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Abstract: Cardiac surgery can be complicated by postoperative bleeding and a need for blood transfusion and surgical re-exploration. Anti-fibrinolytic drugs such as aprotinin and tranexamic acid may reduce bleeding risks but could possibly increase thrombotic complications. Aprotinin, in particular, has recently been implicated in at least two large observational studies, but this could be because it is more widely used in high-risk cardiac surgical patients. Observational studies are prone to several important sources of bias, in particular, confounding by indication (high-risk patients are more likely to receive aprotinin and more likely to have postoperative complications, irrespective of their exposure to aprotinin). Although multivariate adjustment and propensity score-matching can adjust for confounding, there is no certainty that it removes all such bias. For all anti-fibrinolytic drugs, it remains unclear as to whether the beneficial effect on reduced bleeding outweighs a possible increased risk of thrombotic complications. Debate will continue until we have the results of definitive large randomized trials powered to detect a clinically important effect on outcome. **Keywords:** anti-fibrinolytics, aprotinin, evidence, bias. *JECT. 2007;39:308–310*

Complications of cardiac surgery include the competing risks of thrombosis [myocardial infarction (MI), stroke, and venous thromboembolism] and excessive bleeding (1,2). Excessive bleeding after bypass is arguably the most common complication of cardiac surgery, and this can delay completion of surgery, tracheal extubation, and intensive care discharge (2). Some patients require surgical re-exploration. About one half of all cardiac surgical patients receive a blood transfusion, and ~10% of all blood transfusions are used in cardiac surgery (3). Anti-fibrinolytic drugs such as aprotinin and tranexamic acid (TxA) may reduce bleeding risks but could possibly increase thrombotic complications after cardiac surgery.

There is strong evidence from meta-analyses of randomized trials that anti-fibrinolytic therapy with aprotinin reduces blood loss and the need for blood transfusion and re-operation for bleeding in many types of cardiac surgery (4,5). However, there are anecdotal reports (6–11), findings from small trials (12–14), and large observational studies (15,16) to suggest that anti-fibrinolytic drugs increase the risk of myocardial ischemia and thrombotic complications such as graft occlusion, MI, and renal dysfunction. Although aprotinin is the most frequent anti-fibrinolytic drug implicated, there is also some concern with ε-aminocaproic acid (8,13) and desmopressin (5).

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A large retrospective observational study involving 4374 patients undergoing coronary artery bypass graft (CABG) surgery found that aprotinin was associated with increased risk of renal impairment, MI, stroke, and death (15). In a similarly designed study, Karkouti et al. (16) reported on 898 patients undergoing high bleeding risk cardiac surgery, comparing aprotinin with TxA. Unlike the previous study, they found comparable rates of MI in the two groups, however, they did identify an association between aprotinin and renal dysfunction.

These publications have received widespread coverage in the media and have been applauded (17) and criticized (18–20) in the medical literature. Observational studies are prone to several important sources of bias (21–23). Because there is a lack of random allocation to groups, observational studies require some method(s) of balancing factors that may affect the outcome of interest. A recently developed and increasingly used method is the propensity score (24). Here, regression techniques can be used to estimate the probability that, based on that individual's potential confounders, that individual would be in the intervention group or comparison group. If all patients with a similar treatment probability are batched, the actual treatment group approaches that of random allocation—that is, propensity scoring attempts to recreate a random decision process.

However, propensity matching cannot alleviate all bias

and confounding. In the above studies (15,16), the clinical indication for using aprotinin (as opposed to TxA or no anti-fibrinolytic) could be directly correlated with increased risk of renal impairment and MI—in other words, high-risk patients are more likely to receive aprotinin and are more likely to have postoperative complications. This is called confounding by indication. Multivariate adjustment and propensity matching techniques can only adjust for known, measured factors—you cannot adjust for what you do not know or have not measured (23). An illustration of such methods can be found in a controversial study published in 1996 (25), whereby the authors concluded that the use of a pulmonary artery catheter in intensive care was associated with increased mortality and increased utilization of resources. Subsequent large randomized trials could not replicate the findings of the observational study that had used propensity scores to adjust for confounding (26,27).

There are inconsistencies in the Mangano data (20), and the results are not supported by other high level evidence. Three meta-analyses of randomized trials have found that anti-fibrinolytic therapy reduces blood loss, the need for blood transfusion, and re-operation for bleeding in many types of cardiac surgery (5,28,29). Levi et al. (5) did a systematic review and meta-analysis of 72 trials (8409 patients) of anti-fibrinolytic drug therapies. They found that there was a significant decrease in perioperative blood loss and blood transfusion, but also a beneficial effect on the need for re-operation and overall mortality. Specifically, treatment with aprotinin decreased mortality almost twofold [odds ratio (OR), 0.55; 95% confidence interval (CI): 0.34–0.90] compared with placebo. Treatment with aprotinin and with lysine analogs decreased the frequency of re-operation (OR, 0.37; 95% CI, 0.25–0.55 and OR, 0.44; 95% CI, 0.22–0.90, respectively). Aprotinin and lysine analogs did not increase the risk of perioperative MI, but desmopressin was associated with a twofold increase in the risk of MI. Recently, published guidelines from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists have critiqued the latest evidence and made up-to-date recommendations for use of anti-fibrinolytics in cardiac surgery (4).

However, despite the reassurance of numerous clinical trials, even pooled analyses (5,28,29) have insufficient power to identify uncommon but serious adverse outcomes from anti-fibrinolytic therapy (17). Subgroup analyses from a large multicenter trial suggested aprotinin could increase the risk of graft thrombosis in patients with poor distal coronary perfusion (12). Possible factors associated with increased thrombotic complications include insufficient heparinization (30), use of low-dose aprotinin (31), small caliber coronary anastomoses (30), anti-thrombin deficiency (32), and factor V deficiency (33). However, there is also evidence that aprotinin inhibits various prothrombotic pathways and has anti-platelet activity (34). These mechanisms have been used to explain the reduction in cerebrovascular events seen with aprotinin in a meta-analysis of clinical trials (32). Also, aprotinin has been shown to reduce myocardial ischemia-reperfusion injury (35). TxA does not share aprotinin's capacity to inhibit thrombin production (36).

Anti-fibrinolytics are recommended for re-operative and other complex cardiac surgery. However, it is not yet clear whether these drugs provide any benefit beyond limiting blood loss (37) and, for aprotinin at least (4,5), re-exploration for postoperative bleeding. For all anti-fibrinolytic drugs, it remains unclear whether the reduced bleeding outweighs the risk of increased thrombotic complications.

At present, however, there is insufficient evidence to make any reliable statements regarding risks and benefits of aprotinin or TxA in most cardiac surgical procedures (29). Two ongoing large randomized trials should provide some answers (38,39).

The Canadian BART Study

This trial is studying blood conservation using anti-fibrinolytics in cardiac surgery (38). They are comparing aprotinin with the lysine analogs (TxA or ε-aminocaproic acid) in 3000 patients. The primary aim is to measure the effect on excessive bleeding and need for blood transfusion.

The Australian ATACAS Trial (www.atacas.org.au)

The ATACAS Trial is a randomized, double-blind, trial testing whether aspirin, TxA, or both can reduce mortality and/or major morbidity after CABG surgery (39). It is being conducted by the ANZCA Trials Group and is designed to answer two clinically important questions:

i. Should aspirin be continued up until the day of CABG surgery?
ii. Should TxA be used for all at-risk CABG surgeries?

The trial is recruiting 4600 CABG (on-pump or off-pump) patients, comparing TxA vs. placebo and aspirin vs. placebo, in a factorial design, aiming to detect a 30% or greater reduction in major complications or death ($\alpha = 0.05$, $\beta = 0.10$).

CONCLUSIONS

Anti-fibrinolytics reduce bleeding after cardiac surgery, and this probably reduces the need for blood transfusion (28,29). Possible thrombotic risks associated with aprotinin, such as MI and stroke, may or may not be shared by other anti-fibrinolytic drugs (29). Should anti-fibrinolytic therapy (aprotinin or TxA) be used more widely, selec-

tively, or not at all? Debate will continue until we have the results of definitive large randomized trials.

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A "Virtual" Blood Gas Electrode for Use During Cardiopulmonary Bypass

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INTRODUCTION

We describe the development of a "virtual" blood gas electrode system intended for use during cardiopulmonary bypass (CPB). The electrode functions in real time and predicts the patient's arterial and mixed venous blood gas results every 500 ms. It takes as its primary inputs the settings of the heart-lung machine (FiO_2, sweep gas rate, pump flow) and the patient's hematocrit and metabolic rate. The electrode system incorporates integrated computer models of the oxygenator in use during the case and the patient's arterial, venous, and tissue pools. The architecture of the model is a development of that described by Dickinson (1) and is shown schematically in Figure 1.

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EVALUATION

The electrode is currently being validated in vitro against existing physio-logical computer models and in vivo using a Terumo CDI 500 (Terumo Cardiovascular Systems Corp., Ann Arbor, MI) blood gas analyzer (Figure 2). Preliminary results suggest that the performance of modern, hollow fiber artificial lungs is remarkably consistent and is amenable to modeling as described by Riley and Cournand (2).

OTHER APPLICATIONS

The electrode has other possible applications in perfusion practice. These include evaluation of therapeutic

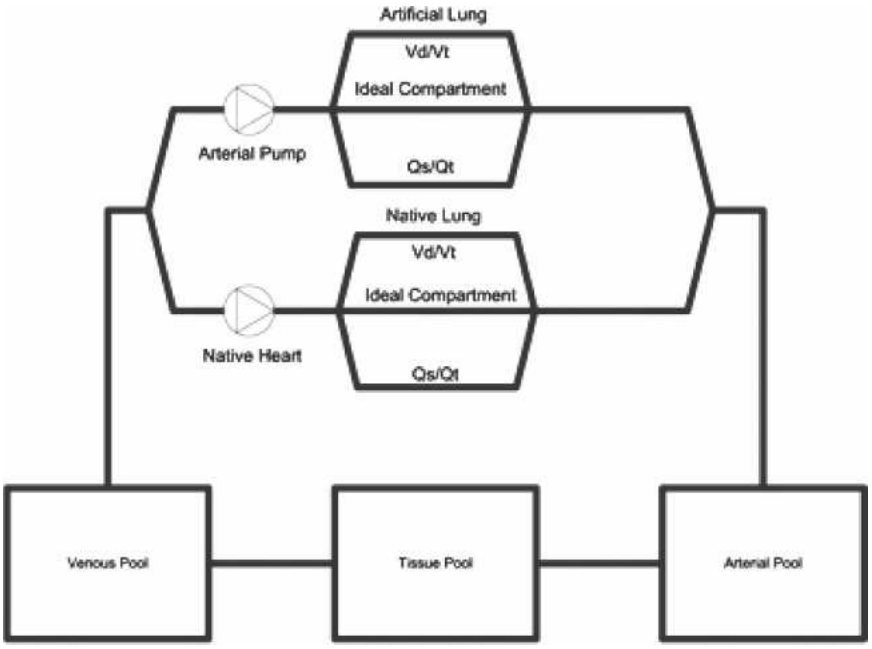

Figure 1. Virtual blood gas electrode system architecture.

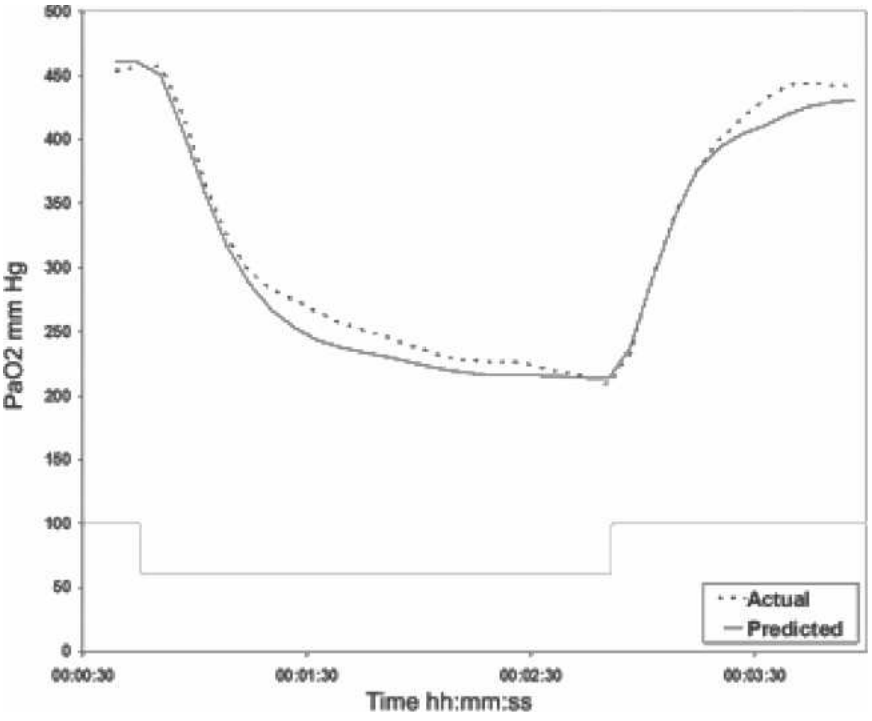

Figure 2. An example of a real-time prediction of PaO_2. In a patient on stable CPB at 32°C the effect of reducing the inspired oxygen concentration from 100%–61% has been demonstrated. The PaO_2 measured by an inline CDI 500 (dotted line) has been compared with the PaO_2 prediction of the virtual electrode (solid line). During the period of exposure to the lower FiO_2, note how the PaO_2 falls from about 460 mmHg to about 230 mmHg in both cases.

strategies, use in simulation systems, use in intelligent alarm systems, and evaluation of new products or techniques.

During the course of the presentation, examples of the evaluation of therapeutic strategies (such as the impact of different degrees of hypothermia on the survivability of arrest) will be examined. The use of the electrode in a software implementation of a veno-venous extracorporeal membrane oxygenation (ECMO) simulation system will also be demonstrated.

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Improving Cardiac Surgery: Does Continuous Blood Gas Monitoring Have a Role to Play?

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INTRODUCTION

The CDI-500 (Terumo Cardiovascular Systems Corp., Ann Arbor, MI) in-line blood gas monitoring device has been in clinical practice for more than a decade. Few randomized studies have evaluated the value of this device with respect to improved perfusion management. We routinely use automated continuous quality indicator programs at our institutions to assess perfusion management.

AIM

The aim of this study was to investigate in a prospective randomized trial the role of in-line blood gas monitoring in the improvement of blood gas management during cardiopulmonary bypass (CPB), using continuous quality indicators.

METHODS

One hundred patients were randomized into two groups before entering the operating room. Group 1 received our standard CPB blood gas management, with intermittent blood gases measured on an ABL700 blood gas machine (Radiometer, Copenhagen, Denmark). Continuous blood gas measurements from the CDI-500 were recorded at 20-second intervals on our data management system; however, the perfusionist was blinded to these measurements. Group 2 received our standard CPB blood gas management; in addition to continuous blood gas measurements visible on the CDI-500, the alarm system activated and the data recorded on our data management system.

Perfusion management for all cases was guided by institutional protocols; specifically, pCO_2 was targeted within the range of 35–45 mmHg. The study was approved by the Bellbury Human Research Ethics Committee.

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RESULTS

There were no differences between the groups in any preoperative factors, procedure types, intraoperative factors, or clinical outcome measures (ventilation time, length of stay, renal failure, mortality). There was a significant reduction in the percentage of CPB that pCO_2 was outside of protocol in group 2 compared with group 1 (Mann-Whitney U test; $z = -2.0446$; $p = .041$). This was most apparent for $pCO_2 > 45$ mmHg, which was 2.5% in group 1 (median, average 10.4%; range, 0%–80%) compared with 1.1% in group 2 (median, average 2.7%; range, 0%–40%; $z = -2.947$; $p = .003$), resulting in 84% quality indicator compliance in group 2 compared with 62% in group 1 ($p = .013$).

DISCUSSION

Continuous blood gas monitoring with the CDI-500 results in significantly improved blood gas management as determined by adherence to institutional protocols.