An evidence-based review of the practice of cardiopulmonary bypass in adults: A focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response

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Cardiopulmonary bypass (CPB) can be used during cardiac surgery to oxygenate and subsequently recirculate blood that has been diverted from the heart and lungs. The practice of CPB has changed—and continues to change—dramatically since its advent in the 1950s. Although structured reviews of the evidence supporting the practice of cardiac surgery have been in the literature for more than a decade and continue to be refined in the wake of new and emerging evidence,^{E1,E2} additional targeted reviews, focusing on issues such as minimizing the effect of the inflammatory response or minimizing neurologic injury, are warranted.^{E3-E5} Previous attempts, by Edwards and colleagues^{E6} and Bartels and associates,^{E7} at synthesizing the evidence base to support the principles of CPB have selectively reviewed the cardiac surgery literature or focused on unique patient populations. Additionally, the development of these reviews has not involved all members of the clinical team, most notably the individuals tasked with operating the CPB circuit. This gap in knowledge is in stark contrast with the shared goal of the cardiac team, namely to improve the conduct of CPB to reduce the patient's risk of adverse outcomes caused by cardiac surgery.

Despite a preponderance of evidence supporting key principles of managing safe and effective CPB practice, wide variation in the use of technology and techniques for conducting CPB persists regionally and nationally.^{E8,E9} Variations in practice have previously been shown to be associated with increased costs, lengths of stay, neurologic injury, and mortality.^{1-3,E5,E10,E11} This variation might be attributed to clinical uncertainty or institutional or local practice standards. To reduce this unwanted practice variation, we must provide our clinical colleagues with critically evaluated and evidence-based review for conducting CPB.

What follows is an evidence-based review for conducting safe, patient-centered, and effective CPB practice. The authors have graded the level of evidence and classified the findings listed below by using the criteria promulgated by the American Heart Association and the American College of Cardiology Task Force on Practice Guidelines (Table 1). The development of these findings evolved from a structured MEDLINE search coupled with critical review of the peer-review literature and debates stemming from presentations at regional and national conferences, including the Connecticut Society of Perfusion (2004), Outcomes 2004: The Key West Meeting, New York State Society of Perfusion (2004), 12th Annual Meeting on Optimization of Blood Management During Surgery (2004), Florida State Society of Perfusion (2004), Tennessee State Society of Perfusion (2004), American Academy of Cardiovascular Perfusion (2005, 2006), and Outcomes 2005: The Key West Meeting.

The authors, a multidisciplinary group of physicians, epidemiologists, and perfusionists, seek to develop and share evidence-based reviews for conducting CPB through rigorous, structured, and expert-driven analysis of the peer-reviewed liter-

Table 1. Methodologies and policies from the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Classification of recommendations	Level of evidence
Class I: Conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective	Level A: Data derived from multiple randomized clinical trials
Class II: Procedure-treatment should be performed-administered	Level B: Data derived from a single randomized trial or nonrandomized studies
Class IIA: Additional studies with focused objectives needed	Level C: Consensus opinion of experts
Class IIB: Additional studies with broad objectives needed; additional registry data would be helpful	
Class III: Procedure-treatment should not be performed-administered because it is not helpful and might be harmful	

Adapted from Eagle KA, Guyton RA, Davidoff R, et al, ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery); 2004.

ature. The mission of this group is to promote literature-supported and evidence-based perfusion practice to improve patient care and enhance clinical outcomes.

We present this as the first of several documents regarding the development of evidence-based review for conducting CPB. In this initial document, regarding the development of evidence-based findings for CPB, we focus on neurologic protection, euglycemia, hemodilution, and the inflammatory response. These findings will be updated to ensure that they continue to be concurrent with emerging evidence and relevant to practicing clinicians.

Methods

The initiative to identify the evidence base and develop findings for perfusion practice evolved from conversations between 2 of the authors (KS, DR). Subsequent conversations between these and other investigators resulted in the development of our study's methodology.

We chose not to conduct a meta-analysis of the peer-reviewed literature, and instead, we adopted a process set forth by the American Heart Association and American College of Cardiology (http://www.acc.org/clinical/manual/manual_1.htm) for the development of evidence-based reviews of the peer-reviewed literature. In short, the group agreed to (1) determine and agree to the scope and clinical objectives, (2) define and conduct appropriate and comprehensive literature searches, (3) sort and evaluate the evidence, (4) synthesize and interpret the evidence, (5) write findings based on expert interpretation of the evidence, (6) assign classification of findings and strength of evidence, and (7) assemble the document. Critical to the success of this project was a detailed and thorough literature search conducted by an expert biomedical librarian (search strategy available by request). Searches were conducted for each of the agreed-upon topics, and results were posted on a customized Web site through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/entrez/>).

Expert reviewers accessed the saved searches through this Web site and used the criteria set forth by the American Heart Association and American College of Cardiology to develop the findings contained herein. The level and class of evidence was applied to

each finding by using a structured literature search of nonanimal studies referenced in MEDLINE. Although animal studies might be referenced within this document, they were not used in the development of the findings. Findings were shared with all coinvestigators and reflect input gathered from presentations at regional, national, and international conferences. Findings for each section were written based on the guidance set forth by the American Heart Association and American College of Cardiology.

Neurologic Protection

Compared with a decade ago, greater numbers of patients of increasing age are surviving more extensive operations, with a shorter duration of hospitalization.^{E12} Despite these advances, a number of fundamental clinical issues continue to be managed by clinical routine, rather than reflecting an optimized CPB strategy for reduction of central nervous system injury. This clinical routine is likely to result in missed opportunities for optimizing care based on the patient's risk of an adverse neurologic outcome.

pH Management

Of fundamental importance in the care of patients undergoing CPB is acid-base status, specifically related to pH management and CO₂ regulation. Since the initial hypothesis that alpha-stat pH management would be associated with improved outcomes,⁴ there have been at least 3 independent prospective randomized trials demonstrating improved neurologic and neuropsychologic outcomes associated with alpha-stat pH management in adult patients undergoing moderately hypothermic CPB.^{1,5,6} Alpha-stat blood gas management preserves cerebral blood flow–metabolism coupling such that hypothermic-induced decreases in metabolic rate are accompanied by proportionate decreases in cerebral blood flow.⁴ The authors do recognize there might be specific circumstances, such as chronic hypercapnia, that might require a modification of this approach to preserve preoperative physiologic levels of Pco₂.

pH Management

The clinical team should manage adult patients undergoing moderate hypothermic CPB with alpha-stat pH management. (Class I, Level A)

Hyperthermia

As reported by Pugsley and coworkers,⁷ a patient's risk of neuropsychologic injury in the setting of coronary artery bypass grafting (CABG) surgery is in part attributed to the quantity of microemboli delivered to the brain. As reported by van der Linden and Casimir-Ahn,^{E13} a high percentage of emboli occur during the early and late phases of cardiac surgery. At the time when patients are most likely to experience an ischemic event, they are typically perfused at warmer temperatures.

Most of the evidence documenting poorer outcomes in the setting of cerebral hyperthermia comes from the stroke literature. Hajat and colleagues^{E14} previously identified an association between cerebral hyperthermia in the setting of stroke with increased morbidity and mortality. Ginsberg and Busto^{E15} elucidated the effect of hyperthermia in the setting of cerebral ischemia, identifying some of these mechanisms: (1) increased release of neurotransmitters, (2) increased free radical production, (3) breakdown of the blood-brain barrier, (4) increased ischemic depolarizations in the focal ischemic penumbra, (5) impaired recovery of energy metabolism and inhibition of protein kinases, and (6) worsening of cytoskeletal proteolysis. Hajat and colleagues,^{E14} in a meta-analysis of the effects of hyperthermia in the setting of stroke, reported increased morbidity and mortality among patients experiencing hyperthermia. In the setting of CABG surgery, Grocott and associates⁸ similarly found postoperative hyperthermia to be associated with greater neuropsychologic dysfunction. Similarly, Grigore and coworkers² found greater neuropsychologic dysfunction in patients randomized to a faster rather than slower rewarming rate in the setting of CABG surgery. Interestingly, patients rewarmed at a faster rate were exposed to higher peak temperatures and a higher mean temperature of greater than 37°C than patients rewarmed slower with lower peak temperatures. Monitoring for and aggressively treating cerebral hyperthermia thus likely offers an opportunity to minimize the exacerbation of neurologic injury in the setting of CABG surgery.

Hypothermia is widely used during CPB to protect the brain and other vital organs by reducing the oxygen requirements of affected tissues. Hypothermic CPB, however, as reported by Insler and colleagues,^{E16} requires a period of rewarming to avoid the adverse outcomes associated with postoperative hypothermia. Contemporary management of CPB, which does not emphasize aggressive monitoring of temperatures, therefore potentially exposes the brain to periods of hyperthermia, as identified by Nathan and Lavalée^{E17} and Cook and associates^{E18} separately. Although

Stone and coworkers^{E19} reported nasopharyngeal monitoring to match well to brain temperature compared with other monitoring sites, Cook and colleagues,^{E18} Grocott and associates,^{E20} Kaukuntla and colleagues,⁹ and Johnson and coworkers^{E21} have noted that it might underestimate jugular venous temperatures and thereby expose the brain to unintended hyperthermia. As documented by Kaukuntla and colleagues,⁹ without monitoring and attentive management, arterial inflow temperatures of the CPB circuit will likely exceed corporeal temperatures and expose the brain to subsequent hyperthermia. It would therefore be advantageous to at least monitor arterial inflow temperature. Caution must be encouraged here because recent work by Salah and associates^{E22} and Newland and coworkers^{E23} has suggested an underestimation of arterial inflow temperature while using conventional coupled temperature-monitoring devices.

Ten randomized controlled trials and 2 prospective cohort studies have evaluated neurologic outcomes associated with temperature management during CPB. Of the 10 randomized controlled trials, 6 (McLean and colleagues,^{E24} The Warm Heart Investigators,^{E25} Engelman and associates,^{E26} Grigore and coworkers,^{E27} Plourde and colleagues,^{E28} and Birdi and associates^{E29}) concluded that there was no difference between normothermic and hypothermic CPB, 3 (Martin and coworkers,^{E30} Mora and colleagues,^{E31} and Regragui and associates^{E32}) reported poorer outcomes with normothermic CPB, and 1 (Grimm and coworkers^{E33}) found poorer outcomes with hypothermic CPB. Three nonrandomized studies reported conflicting findings regarding temperature management and neurologic outcomes, with 1 (Gaudino and colleagues^{E34}) concluding worse outcome with normothermic CPB and 2 (Singh and associates^{E35} and Christenson and coworkers^{E36}) showing no statistical difference. Differences in these findings likely are attributed to heterogeneity in study design, lack of standardized temperature-monitoring sites, and potentially unrecognized cerebral hyperthermia among study patients, regardless of temperature management strategy. The study by Nathan and colleagues¹⁰ is noteworthy in that the group randomized to separate from bypass at 34°C (hypothermic group) most likely avoided any transient hyperthermia. They found a reduction in neuropsychologic deficits in this group compared with the group rewarmed to 37°C, without a concomitant increase in morbidity and mortality.

The measurement and tracking of perioperative hyperthermia is essential for neurologic protection. Cerebral temperatures exceeding 37°C might expose patients to unnecessary neurologic risk. During CPB, reliable and accurate measurement of arterial inflow temperatures is imperative. Preventing hyperthermia and subsequent risk of neurologic injury in this setting might occur through reliable measurement and strict avoidance of perfusion temperatures exceeding 37°C.

Avoidance of Hyperthermia

Limiting arterial line temperature to 37°C might be useful for avoiding cerebral hyperthermia. (Class IIa, Level B)

“Coupled temperature” ports for all oxygenators should be checked for accuracy and calibrated.

Minimizing Return of Pericardial Suction Blood

As noted separately by Caguin and Carter,¹¹ Clark and associates,^{E38} and Siderys and coworkers,^{E39} reinfusion of cardiomy suction blood exposed to pericardial and mediastinal surfaces in patients undergoing CPB is associated with postoperative neurologic injury, attributed in part to increased levels of hemolysis and fat in scavenged blood. Brooker and colleagues^{E40} identified the association between cerebral lipid microemboli after CPB with the reinfusion of cardiomy suction blood in a canine model. Additionally, Appelblad and Engstrom,^{E41} Kaza and associates,¹² Jewell and coworkers,¹³ and de Vries and colleagues^{E42} identified pericardial suction blood as the primary source of fat emboli during CPB. De Hann and associates¹⁴ demonstrated that reinfusion of pericardial suction blood exacerbated activation of markers of coagulation and fibrinolysis and resulted in increased blood loss. Spanier and coworkers^{E43} documented increased endotoxin levels with the reinfusion of pericardial suction blood during CPB, whereas research conducted by Chung and colleagues,¹⁵ Johnell and associates,^{E44} and Weerwind and coworkers^{E45} reported the following sequelae: thrombin generation and activation of the coagulation, fibrinolytic, and inflammatory pathways.

To reduce systemic inflammatory response and exposure to fat emboli, techniques to minimize shed mediastinal blood through improved intraoperative hemostasis should be advocated, and where possible, reinfusion of pericardial suction blood should be avoided. Secondary filtration of pericardial suction blood, as well as treatment with a blood cell processor with or without additional filtration before return to the extracorporeal circuit, has resulted in reduced reinfusion of fat emboli, as noted by Kaza and associates,¹² Jewell and coworkers,¹³ de Vries and colleagues,^{E42} and Kincaid and associates.^{E46}

Return of Pericardial Suction Blood

Direct reinfusion to the CPB circuit of unprocessed blood exposed to pericardial and mediastinal surfaces should be avoided. (Class I, Level B)

Blood cell processing and secondary filtration can be considered to decrease the deleterious effects of reinfused shed blood. (Class IIb, Level B)

Aortic Assessment

As noted by Likosky and associates,^{E47} among others, cerebral atheroemboli account for the majority of type I (stroke) outcomes after CABG surgery, with noncalcific

plaque likely the greatest contributor of these emboli. Davila-Roman and colleagues¹⁶ reported that noncalcific plaque, unfortunately, is least likely to be identified by intraoperative surgical palpation of the aorta before instrumentation. Blauth and coworkers^{E48} and Davila-Roman and associates^{E49} have shown that advanced age, diabetes mellitus, and vascular disease, all conditions that are well-known risk factors for perioperative stroke, are also predictors of advanced aortic atherosclerosis and attendant systemic atheroemboli. Mizuno and colleagues^{E50} and Davila-Roman and associates^{E49} identified significant atherosclerosis (defined as intimal thickening >5 mm in the aortic arch), present in up to 20% of patients undergoing CABG, to be associated with an increased risk of stroke after CABG, presumably through an embolic mechanism, as suggested by Djaiani and colleagues.^{E51} As reported by Davila-Roman and colleagues,¹⁶ epiaortic ultrasonography is significantly more sensitive than transesophageal echocardiography (TEE) for identification of atherosclerosis of the ascending aorta, whereas Sylvis and associates¹⁷ and Royse and coworkers¹⁸ have identified both ultrasonographic techniques to be superior to palpation. Epiaortic ultrasonography and TEE provide complementary information regarding thoracic aortic atherosclerosis. Many reports (Davila-Roman and associates,^{E49} Trehan and colleagues,¹⁹ Gold and coworkers,^{E52} and Mackensen and associates²⁰) have highlighted a protective effect, in terms of prevention of atheroembolic complications, with the modification of surgical technique on the basis of results of intraoperative epiaortic ultrasonography and TEE in elderly patients undergoing cardiac procedures. As reported by Gold and coworkers,^{E52} Trehan and colleagues,¹⁹ Ribakove and associates,^{E53} and Baribeau and coworkers,^{E54} epiaortic ultrasonography and TEE might facilitate the reduction of neurologic injury through the identification of areas free from atherosclerosis for aortic cannulation, avoidance of the ascending aorta entirely through femoral or axillary artery sites, or use of an off-pump technique.

Aortic Assessment

In patients undergoing CPB at increased risk of adverse neurologic events, strong consideration should be given to intraoperative TEE or epiaortic ultrasonographic scanning of the aorta: (1) to detect nonpalpable plaque (Class I, Level B) and (2) for reduction of cerebral emboli (Class IIa, Level B).

Arterial Line Filtration

The presence of microemboli (gaseous or particulate) and foreign material in the CPB circuit and subsequent delivery to the patient through the arterial line has resulted in the incorporation of arterial filters into CPB circuits. Although in vitro and in vivo studies by Taylor and coworkers^{E55} and Loop and associates,²¹ respectively, have provided evidence for benefits associated with the inclusion of these filters into

the arterial line, their routine use in the CPB circuit is not universal.^{E56}

Pugsley and colleagues⁷ and Padayachee and coworkers²² demonstrated a reduction in embolic load delivered to the brain with the inclusion of arterial line filters, whereas Sellman and associates²³ similarly demonstrated a reduction in emboli distal to the arterial line filter. Padayachee and coworkers²² additionally demonstrated an advantage with 25- versus 40- μ m filters in removing gaseous microemboli.

Most studies reporting on the benefits of filtration were performed with bubble oxygenators. In one randomized trial Pugsley and colleagues⁷ showed a reduction in neuropsychologic injury with a 40- μ m arterial line filter, a finding that both Aris and coworkers^{E57} and Sellman and associates^{E58} had been unable to demonstrate. In lieu of additional studies focused specifically on the association between the use of arterial filters and neurologic injury, the association between embolic load and neuropsychologic outcome has been demonstrated through reports by Pugsley and colleagues,⁷ Clark and coworkers,^{E59} and Stump and associates.^{E60}

Arterial Filtration

Arterial line filters should be incorporated in the CPB circuit to minimize the embolic load delivered to the patient. (Class I, Level A).

Maintenance of Euglycemia

As argued by Murkin,^{E61} there is both experimental and clinical evidence that hyperglycemia is associated with exacerbation of neurologic injury, as well as a variety of other adverse outcomes, including wound infection and mortality, among critically ill patients. McAlister and colleagues^{E62} correlated average blood glucose levels on the first postoperative day after CABG surgery with a variety of adverse outcomes (stroke, myocardial infarction, septic complication, or death). For each 1-mmol/L increase above 6.1 mmol/L (1 mmol = 18 mg/dL), the risk of these outcomes increased by 17%. In a prospective study of critically ill patients, Finney and associates^{E63} suggested that the control of blood glucose levels, rather than insulin levels per se, accounts for apparent benefits in mortality. In a single-center study by Latham and coworkers^{E64} with an accompanying editorial by Dellinger,^{E65} the greatest risk for surgical site infection among all patients undergoing cardiothoracic surgery occurred among those with either postoperative hyperglycemia (blood glucose levels >200 mg/dL) or undiagnosed diabetes. Estrada and associates²⁴ reported on a historic cohort of 1574 patients undergoing CABG between 1998 and 1999 within a single institution. The authors found perioperative hyperglycemia to be associated with both longer postoperative length of stay and increased hospitalization charges/costs among diabetic and nondiabetic patients.

Furnary and colleagues²⁵ demonstrated, in a nonrandomized, prospective interventional study of 4864 patients undergoing cardiac procedures, that perioperative hyperglycemia is directly associated with increased rates of death, deep sternal wound infections, length of stay, and hospital costs. The work from Furnary and colleagues,^{25,E66-E68} Estrada and associates,²⁴ and McAlister and colleagues^{E62} suggests that a target glucose range of less than 150 mg/dL is favorable for maintaining euglycemia. Recent evidence by Carvalho and coworkers^{E69} suggests that maintenance of intraoperative blood glucose levels might be managed in both diabetic and nondiabetic patients with the use of an aggressive insulin dosing strategy during cardiac surgery.

Ouattara and associates,^{E70} in an observational study of 200 consecutive diabetic patients undergoing cardiac surgery, demonstrated that poor intraoperative control of blood glucose concentrations was associated with an increased incidence of in-hospital morbidity (including cardiovascular, infectious, neurologic respiratory, neurologic, and renal). Two additional observational studies (Gandhi and coworkers²⁶ and Doenst and associates²⁷), representing a combined 6689 patients undergoing cardiac surgery, demonstrated a relationship between intraoperative hyperglycemia and mortality.

In a systematic review of the evidence authored by Garber and coworkers,^{E71} the position statement on inpatient diabetes and metabolic control, sponsored by The American College of Endocrinology, the American Association of Clinical Endocrinologists, and the cosponsoring organizations (including the Society of Thoracic Surgeons), supports the need for early detection and aggressive management of hyperglycemia in the hospital setting for improving patient outcomes.

Groban and associates^{E72} identified increased blood sugar as a routine accompaniment to CPB, reflecting in part the difficulty in effectively treating hyperglycemia, especially in the presence of intense gluconeogenesis and insulin resistance, such as during CPB. As suggested by Murkin,^{E61} avoidance or limitation of some of the following might effectively limit hyperglycemia with the expectation of enhanced neurologic outcomes: (1) glucose containing intravenous, cardioplegic, and pump-priming solutions; (2) enhanced awareness and treatment of catecholamine-induced hyperglycemia; and (3) more aggressive insulin dosing strategies.

Maintenance of Euglycemia

The clinical team should maintain perioperative blood glucose concentration within an institution's normal clinical range in all patients, including nondiabetic subjects. (Class I, Level B)

Modified Extracorporeal Circuits

Hemodilution

Currently, the advancement of perfusion technology has led to the development and use of condensed circuits and bio-

passive surface modification. The goal of these efforts has been to reduce the systemic inflammatory response syndrome (SIRS) while preserving platelet function and minimizing the need for allogeneic blood products.

Several large observational studies (DeFoe and colleagues,³ Habib and associates,²⁸ Fang and coworkers,²⁹ and Karkouti and colleagues³⁰) have identified an association between nadir hematocrit (HCT) values and risk of in-hospital mortality and other adverse events. DeFoe and colleagues³ reported results from a multicenter study of 6980 patients undergoing isolated CABG surgery. Patients experiencing a single HCT value of 19% or less during CPB had more than twice the mortality as patients with a nadir HCT value of 25%. Furthermore, the lowest HCT value during CPB was significantly associated with increased intraoperative or postoperative placement of an intra-aortic balloon pump and return to CPB after attempted separation. Habib and associates²⁸ retrospectively analyzed 5000 patients undergoing cardiac operations with CPB and found that stroke, myocardial infarction, low cardiac output, cardiac arrest, renal failure, prolonged ventilation, pulmonary edema, reoperation caused by bleeding, sepsis, and multi-organ failure were all significantly and systematically increased as the lowest HCT value decreased to less than 22%. In a study of 2738 patients undergoing isolated CABG, Fang and coworkers²⁹ found an increased risk of postoperative death (odds ratio, 2.7) in patients with HCT values of 14% or less, and in a high-risk subgroup there was an increased risk (odds ratio, 2.2) when the HCT value during CPB was less than 17%. Karkouti and colleagues³⁰ examined a series of 10,949 patients undergoing on-pump CABGs and found that the risk of a perioperative stroke increased 10% with each percentage decrease in nadir HCT value (95% confidence interval, 4%-18%; $P = .002$).

Additional studies (Karkouti and associates^{E73} and Swaminathan and coworkers^{E74}) have also identified the association between nadir HCT values and renal injury. Karkouti and associates^{E73} analyzed 9080 consecutive patients undergoing cardiac operations with CPB and found an independent and nonlinear relationship between the nadir HCT value during CPB and acute renal failure, necessitating dialysis support. Swaminathan and coworkers,^{E73} in a study of 1404 patients undergoing primary elective CABG, found both a significant interaction between the lowest HCT value during CPB and body weight and between HCT value and postoperative creatinine increase level.

The observations listed above warrant the application of techniques to reduce the incidence of low HCT values. Several studies (McCusker and associates,^{E75} Cormack and colleagues,^{E76} Beholz and coworkers,^{E77} van Boven and associates,^{E78} Takai and colleagues,^{E79} and Shapira and coworkers^{E80}) have illustrated that a reduction in surface area-priming volume of the CPB circuit reduces the fre-

quency of low HCT values and subsequently reduces the incidence of allogeneic blood transfusions. Additionally, as evidenced by Rosengart and associates,^{E81} Balachandran and colleagues,^{E82} and Petry and coworkers,^{E83} the technique of retrograde autologous priming of the CPB circuit is an effective means to decrease significantly hemodilution and the frequency of red cell transfusion during cardiac operations. As documented by Speiss,^{E84} the untoward effects of allogeneic blood transfusions have been well documented in more than 3000 articles published in the medical literature. The adverse sequelae of transfusing red blood cells include infection (Chelemer and colleagues^{E85} and Leal-Noval and coworkers^{E86}), renal injury and acute renal failure (Habib and coworkers^{E87}), increased length of stay (Leal-Noval and coworkers,^{E86} Vamvakas and Carven,^{E88} and Fransen and associates^{E89}), and mortality (Leal-Noval and coworkers^{E86} and Michalopoulos and associates^{E90}).

Kuduvalli and colleagues³¹ prospectively studied 3024 patients undergoing CABG and concluded that transfusion increased both 30-day (1.9% vs 1.1%, $P < .05$) and 1-year mortality (adjusted hazard ratio, 1.88; 95% confidence interval, 1.23-3.00; $P < .01$).³¹ Engoren and coworkers^{E91} examined the long-term effects of transfusion and found it to be a significant predictor of mortality at 5 years.

Reduction of Hemodilution

Efforts should be made to reduce hemodilution, including reduction of prime volume, to avoid subsequent allogeneic blood transfusion. (Class I, Level A)

Attenuation of the Inflammatory Response

The risk of SIRS and complement activation caused by CPB has been well described by Kirklin and associates^{E92} and Ascione and coworkers.^{E93} Previous research by Ishikawa and colleagues,^{E94} Striggow and associates,^{E95} and Baufreton and coworkers^{E96} has reported the association between the inflammatory processes and exacerbation of ischemic brain injury by various mechanisms, including increased capillary permeability, complement activation, neutrophil activation, and protease-activated receptor upregulation. Blood contact with nonbiocompatible surfaces of the CPB circuit was implicated by Butler and associates^{E5} as a cause of the SIRS. A number of commercially available extracorporeal devices, including biocompatible surface coatings, condensed (miniaturized) extracorporeal circuits, and leukocyte-depleting filters, have demonstrated a suppression of the inflammatory response to extracorporeal circulation and improved outcomes. Administration of specific anti-inflammatory pharmacologies has also been associated, by Sedrakyan and coworkers³² and Asimakopoulos and colleagues,^{E97} with decreased inflammatory processes and improved clinical outcomes.

The decrease in the incidence of SIRS with the use of biocompatible surface technology is well documented by

Saito and associates,^{E98} Videm and coworkers,^{E99} Fromes and colleagues,^{E100} and Moen and associates.^{E101} In addition, Defraigne and coworkers^{E102} and Rubens and colleagues^{E103} documented platelet preservation with the use of biocompatible surface additive-coated CPB circuits. Although several randomized clinical trials (Dickinson and colleagues,^{E104} Mahoney and Lemole,³³ McCarthy and coworkers,^{E105} Mongero and associates,^{E106} and Ranucci and colleagues³⁴) demonstrated improved outcomes with the use of biocompatible circuits, one by Muehrcke and associates^{E107} was unequivocal in its findings. Ranucci and colleagues³⁴ conducted a multicenter randomized trial evaluating the effect of heparin-coated circuits on clinical outcomes among 886 patients undergoing cardiac operations. Heparin-coated circuits resulted in a shorter intensive care unit (ICU) and postoperative length of stay and fewer “severely impaired clinical outcomes” (defined as ICU length of stay >5 days or death). McCarthy and coworkers^{E105} randomized 350 patients undergoing CABG reoperations with or without valve operations to receive either heparin-coated or uncoated CPB circuits. The investigators’ protocol included full-dose heparin, an open reservoir, and cardiomyotomy suction. The percentage of major bleeding episodes was significantly less with heparin-coated circuits. In a prospective randomized study of 61 patients undergoing elective cardiac surgery with CPB, Heyer and coworkers^{E108} found that patients treated with heparin-bonded CPB circuits had less postoperative cognitive dysfunction. Furthermore, a meta-analysis by Mahoney^{E109} has provided evidence of clinical benefits and cost savings with the use of heparin-bonded circuits. Finally, the combination of a condensed circuit with biocompatible surface additive coating has been associated (McCusker and associates,^{E75} Fromes and coworkers,^{E100} and Wiesenack and colleagues³⁵) with reduced ventilator time, ICU and hospital length of stay, and transfusion requirements.

Attenuation of the Inflammatory Response

Reduction of circuit surface area and the use of biocompatible surface-modified circuits might be useful-effective at attenuating the systemic inflammatory response to CPB and improving outcomes. (Class IIa, Level B)

Discussion

We have made every effort to develop findings for perfusion practice that are grounded in evidence-based medicine. We adopted a previously validated method for explicitly reviewing and grading the level and class of evidence as it relates to neurologic injury, euglycemia, hemodilution, and the inflammatory response. These findings will be updated on a routine basis, including the addition of other practice items, to keep them contemporaneous with the peer-

reviewed medical literature and useful and pertinent to practicing clinicians.

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