

# Optimal Perfusion During Cardiopulmonary Bypass: An Evidence-Based Approach

Glenn S. Murphy, MD\*

Eugene A. Hessel II, MD†

Robert C. Groom, MS, CCP‡

In this review, we summarize the best available evidence to guide the conduct of adult cardiopulmonary bypass (CPB) to achieve “optimal” perfusion. At the present time, there is considerable controversy relating to appropriate management of physiologic variables during CPB. Low-risk patients tolerate mean arterial blood pressures of 50–60 mm Hg without apparent complications, although limited data suggest that higher-risk patients may benefit from mean arterial blood pressures >70 mm Hg. The optimal hematocrit on CPB has not been defined, with large data-based investigations demonstrating that both severe hemodilution and transfusion of packed red blood cells increase the risk of adverse postoperative outcomes. Oxygen delivery is determined by the pump flow rate and the arterial oxygen content and organ injury may be prevented during more severe hemodilutional anemia by increasing pump flow rates. Furthermore, the optimal temperature during CPB likely varies with physiologic goals, and recent data suggest that aggressive rewarming practices may contribute to neurologic injury. The design of components of the CPB circuit may also influence tissue perfusion and outcomes. Although there are theoretical advantages to centrifugal blood pumps over roller pumps, it has been difficult to demonstrate that the use of centrifugal pumps improves clinical outcomes. Heparin coating of the CPB circuit may attenuate inflammatory and coagulation pathways, but has not been clearly demonstrated to reduce major morbidity and mortality. Similarly, no distinct clinical benefits have been observed when open venous reservoirs have been compared to closed systems. In conclusion, there are currently limited data upon which to confidently make strong recommendations regarding how to conduct optimal CPB. There is a critical need for randomized trials assessing clinically significant outcomes, particularly in high-risk patients.

(Anesth Analg 2009;108:1394–417)

**T**otal cardiopulmonary bypass (CPB) has been used for cardiac surgery for over half a century and is used successfully thousands of times each day worldwide. Although most patients tolerate the procedure reasonably well, subtle as well as clinically apparent evidence

of its harm are often encountered (e.g., excessive bleeding, systemic inflammation, strokes and neuropsychological dysfunction, renal, pulmonary, and cardiac dysfunction and multiorgan failure). The techniques for conducting CPB were developed based upon physiologic principles using materials which were available at that time, followed by animal testing and eventually clinical trials.<sup>1,2</sup> Over the past five decades, numerous advancements in equipment and techniques have been introduced with notable improvements in morbidity and mortality.

Although some of these changes have been introduced based upon logical principles, laboratory investigations and clinical studies, more often, these changes have been driven by the personal biases, clinical impressions, experiences of individual cardiac surgical groups, and industry pressures. This has resulted in major differences in practice among teams conducting CPB.<sup>3</sup>

A new paradigm of medical practice, evidence-based medicine, has emerged which encourages clinical practice based upon objective clinical evidence. This paradigm posits that there is a hierarchy of strength or quality of evidence and that practice should be guided by the highest level of available

---

From the \*Department of Anesthesiology, Evanston Northwestern Healthcare and Northwestern University Feinberg School of Medicine, Evanston, Illinois; †Department of Anesthesiology and Surgery (Cardiothoracic), University of Kentucky College of Medicine, Lexington Kentucky; and ‡Department of Cardiovascular Perfusion, Maine Medical Center, Portland, Maine.

Accepted for publication June 1, 2008.

Supported by Department of Anesthesiology, Evanston Northwestern Healthcare; Department of Anesthesiology and Cardiovascular Surgery, University of Kentucky College of Medicine, Department of Cardiovascular Perfusion, Maine Medical Center.

Robert Groom has received research grants or equipment from the Sorin Group, Somanetics Corporation, Spencer Technology, And Terumo Cardiovascular.

Address correspondence and reprint requests to Glenn S. Murphy, MD, Department of Anesthesiology, Evanston Northwestern Healthcare, 2650 Ridge Ave., Evanston, IL 60201. Address e-mail to dgmurphy2@yahoo.com.

Copyright © 2009 International Anesthesia Research Society  
DOI: 10.1213/ane.0b013e3181875e2e

**Table 1.** Classification of Recommendations

Class I:	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II:	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment IIa. Weight of evidence/opinion is in favor of usefulness/efficacy IIb. Usefulness/efficacy is less well established by evidence/opinion
Class III:	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful
Level of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials
Level of evidence B	Data derived from a single randomized trial, or nonrandomized studies
Level of evidence C	Consensus opinion of experts

Classification of recommendations based on the system developed by the Joint Task Force for Guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA).

Available at: [http://circ.ahajournals.org/manual/manual\\_1lstep6.shtml](http://circ.ahajournals.org/manual/manual_1lstep6.shtml).

evidence. Unfortunately, a review of the literature by the working group on Extra Corporal Circulation and Mechanical Ventricular Assist Devices of the German Society of Thoracic and Cardiovascular Surgery reached the pessimistic conclusion that little of the practice of CPB was based upon evidence of a high enough level to allow recommendations to be made.<sup>3</sup> The purpose of this review is to summarize the best evidence available to guide the conduct of adult CPB. The classification system used to evaluate the level of evidence and summarize the findings is based on criteria developed by the Joint Task Force for Guidelines of the American College of Cardiology and the American Heart Association (Table 1). The first part of the review will concentrate on the major hemodynamic and oxygen delivery variables of CPB and the second part on the major components of the extracorporeal circuit (ECC). Obviously, more than conduct of CPB influences outcome (e.g., preoperative status, surgical technique and precision, pre- and postoperative care, rehabilitation, and family support). These factors must be carefully controlled in any study assessing the effect of any aspect of the conduct of CPB on patient outcome.

### DEFINING OPTIMAL PERFUSION DURING CPB

There is no generally accepted definition of optimal perfusion and there is a continuum of quality of

outcome starting from adequate, sufficient, or minimally acceptable, progressing through superior, and reaching optimal or maximal.<sup>4</sup> Perfusion could be considered minimally acceptable if the patient survives without life-threatening complications or persistent clinically manifest organ dysfunction. This definition is affected by how long survival is monitored, and by how carefully organ function is assessed. The assessment of neurological outcome is a good example of the complexity associated with defining outcome. The intensity of evaluation can range from the cursory examination by the surgeon during postoperative visits, examination by a neurologist, the administration of a battery of neuropsychometric tests, or brain scanning (magnetic resonance imaging/computed tomography). The reported incidence of adverse neurological outcome is progressively higher with the more intense and sensitive evaluations. On the other hand, it might also be asked "If it doesn't bother the patient (or the family), does it matter?"

The primary objective of cardiac surgery is a healthy, productive long-term survivor rather than simply hospital survival and absence of gross organ dysfunction. Thus, for this review, optimal perfusion is defined as that which is followed by the best long-term patient outcome in terms of survival and function of all organ systems (especially the brain, heart, kidney, lungs, the gut and the liver). Optimal perfusion should be associated with minimal activation of inflammation, coagulation, and of the autonomic and endocrine systems, preservation of homeostasis and oncotic pressure, the least morbidity and disturbance of organ function, and the fastest recovery (e.g., shortest time on ventilator, shortest length of stay in intensive care unit and hospital, quickest return to normal activities).

### MANAGEMENT OF PHYSIOLOGIC VARIABLES DURING CPB

CPB represents a unique clinical circumstance in which nearly all aspects of perfusion can be determined by clinicians. Presently, there is considerable controversy relating to appropriate management of physiologic variables during CPB, which has resulted in significant differences in how bypass is conducted in cardiac centers.<sup>5</sup> This section will focus on the primary determinants of tissue oxygen supply and demand, which include mean arterial blood pressure (MAP), bypass flow rates, type of flow (pulsatile versus nonpulsatile), hematocrit values, systemic oxygen delivery ( $DO_2$ ), temperature, and acid-base management.

#### Mean Arterial Blood Pressure

The optimal MAP to ensure adequate tissue perfusion during CPB has not been established. In particular, the lower limit of safe perfusion pressure is uncertain, with investigators advocating lower (50–60 mm Hg) and higher (70–80 mm Hg) mean pressures

**Table 2.** Arterial Pressure Management

Potential advantages of higher MAPs	Potential advantages of lower MAPs
Enhanced tissue perfusion in high risk patients (hypertensive, diabetic, and elderly)	Less trauma to blood elements
Improved collateral flow to tissues at risk of ischemia	Reduction of blood in the surgical field
Allows for higher pump flow rates on CPB	Less cardiotomy suction
	Permits the use of smaller venous and arterial cannulae
	Enhanced myocardial protection (reduced collateral coronary blood flow)
	Reduced embolic load to the CNS (reduced pump flow)

MAP = mean arterial blood pressure; CPB = cardiopulmonary bypass; CNS = central venous system.

during routine CPB. At many cardiac centers, clinicians maintain MAP of 50–60 mm Hg during CPB in the majority of adult patients undergoing bypass. This value is likely based on data supporting a MAP of 50 mm Hg as the lower limit of cerebral autoregulation. Early investigations have suggested that cerebral blood flow (CBF) remains relatively constant at MAPs between 50–150 mm Hg.<sup>6,7</sup> The lower limit of cerebral autoregulation may be as low as 20–30 mm Hg in anesthetized patients during hypothermic CPB using moderate hemodilution.<sup>8,9</sup> Other potential advantages of lower MAPs during CPB include less trauma to blood elements and a reduction in noncoronary collateral flow to the heart (Table 2).

Other data support higher MAPs (>70 mm Hg) during CPB.<sup>10–13</sup> More recent investigations have demonstrated that the lower limit of autoregulation may be much higher than 50 mm Hg. Studies in awake, normotensive adults have demonstrated that the mean lower limit of cerebral autoregulation is 73–88 mm Hg.<sup>10–12</sup> Systemic pressures were reduced using lower extremity negative pressure devices and drugs (trimethaphan or labetalol) and autoregulation assessed by measuring mean CBF velocity with Doppler or arterial-jugular venous oxygen content differences. These studies also noted a more than twofold variability in the lower limit of autoregulation among study patients. Furthermore, the autoregulatory curve may be shifted to the right in the patient with hypertension.<sup>13</sup> Advocates for maintaining higher MAPs on CPB note that many patients presenting for cardiac surgery are older, hypertensive, and have preexisting cerebral vascular disease. Theoretically, perfusion pressures >70 mm Hg may reduce the risk of hypoperfusion in the high-risk patient population and enhance collateral blood flow when emboli impair tissue perfusion.

A large number of prospective observational studies have examined the association between hypotension on CPB (typically defined as a MAP <50 mm Hg) and adverse outcomes postoperatively. The primary outcome variable assessed in many of these clinical trials was neurologic dysfunction (variably defined). Early studies demonstrated that neurologic or neuropsychiatric function was worsened<sup>14–16</sup> or unchanged<sup>17–19</sup> in patients with hypotension during CPB. Larger databased investigations performed since the mid-1980s have also demonstrated conflicting results. In a study of 511 patients undergoing CPB, MAPs <50 mm Hg (expressed as absolute values or intensity-duration units) were not predictors of postoperative renal or neurologic dysfunction.<sup>20</sup> An analysis of outcome data from 2862 coronary artery bypass graft (CABG) patients from a single institution found no evidence to support an association between MAPs <50 mm Hg during CPB and in-hospital mortality.<sup>21</sup> A subsequent analysis of the same database revealed an association between lower MAPs and less neurologic injury.<sup>22</sup> In contrast, Reich et al. identified hypotension during bypass (defined as a MAP <50 mm Hg) as a significant predictor of mortality in a cohort of 2149 CABG patients.<sup>23</sup> In an analysis of 3279 consecutive CABG patients operated on over a 10-yr period, a significant correlation between intraoperative hypotension and postoperative stroke was identified.<sup>24</sup> Fisher et al. observed that patients who developed acute renal failure had longer periods of bypass at pressures <60 mm Hg than control patients with normal postoperative renal function.<sup>25</sup>

In the only randomized trial that has specifically addressed the effect of high versus low MAPs during CPB on major outcomes after cardiac surgery, 248 elective primary CABG patients were randomized to a low pressure (targeted to 50–60 mm Hg) or high pressure (targeted to 80–100 mm Hg) group.<sup>26</sup> The combined incidence of adverse cardiac and neurologic outcomes was lower in the high pressure group (4.8%) compared to the low pressure group (12.9%,  $P = 0.026$ ), but there was not a statistically significant difference in these individual outcomes. Noteworthy was the fact that the average pressure actually achieved in the high pressure group was significantly lower ( $69 \pm 7$  mm Hg) than the targeted pressure, while in the low pressure group the achieved pressure ( $52 \pm 5$  mm Hg) was within the targeted range. In a subsequent *post hoc* analysis of this same cohort of patients, Hartman et al. examined the relationship between MAP management, atheroma grade of the aorta, and the incidence of postoperative stroke.<sup>27</sup> Trends towards an increased risk of stroke were observed in patients with advanced aortic disease managed in the low pressure group (7 of 36 patients) compared to the high pressure group (2 of 30 patients), although these differences were not statistically significant.



**Table 3.** Factors Determining Minimal Safe Pump Flow During Cardiopulmonary Bypass

Body Surface Area (BSA)
Degree of hypothermia
Acid-base balance
Whole-body oxygen consumption
Degree of neuromuscular blockade
Oxygen content of blood (hemoglobin concentration and saturation, PaO <sub>2</sub> )
Depth of anesthesia
Specific organ ischemic tolerance

There is insufficient evidence at the present time to recommend an optimal MAP for all patients undergoing CPB. Despite the publication of numerous clinical trials, several questions remain unanswered. In particular, MAP may be influenced by multiple variables including flow, blood viscosity (temperature and hematocrit), depth of anesthesia, anesthetic used, and perioperative inflammation. MAP can be increased or decreased by altering flow rate or blood viscosity (i.e., hematocrit) and by the administration of vasoactive medications. The impact of these various factors on outcomes complicates interpretation of studies assessing optimal MAP. Furthermore, most clinical studies excluded patients with preexisting cerebrovascular disease. Limited data suggest that autoregulation is impaired in patients with overt cerebral ischemic disorders.<sup>28</sup> The single randomized trial assessing high versus low bypass pressures was not adequately powered to detect differences in mortality or uncommon individual outcomes such as stroke, myocardial infarction (MI), or renal failure.

In the absence of better data, the choice of perfusion pressures during CPB must be based upon an assessment of the benefits and risks of higher and lower MAPs, and decisions about optimal pressure should be determined on a case-by-case basis. Limited data suggest that certain patient populations may benefit from higher pressures on bypass. These groups include patients with advanced atherosclerotic disease of the aorta,<sup>27</sup> the elderly (cognitive decline has been associated with lower MAPs in older patients),<sup>29</sup> hypertensive patients (cerebral autoregulation curve shifted to the right),<sup>30</sup> and patients with diabetes (abnormal cerebral autoregulation during CPB).<sup>31</sup>

### Systemic Bypass Flow Rates

The pump flow required to provide adequate tissue perfusion is influenced by several variables (Table 3). There are no standards for optimal pump flow during CPB, and institutional practices are largely based on empirical experience. Initial flow rates are primarily calculated based upon body surface area and temperature management strategy. The flow rate most commonly used during CPB ( $2.2\text{--}2.5\text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ) approximates the cardiac index of a normothermic anesthetized patient with a normal hematocrit.<sup>32</sup> However, perfusion flows as low as  $1.2\text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$  during

hypothermic bypass have been used by some investigators with good clinical outcomes.<sup>9,33</sup> Proposed advantages of reduced flow rates include less hypertension during hypothermic bypass (due to increased blood viscosity and temperature-induced increases in systemic vascular resistance), improved intracardiac exposure due to less bronchial blood flow retuning to the left heart, and reduced warming of the myocardium via noncoronary collateral vessels. Although some evidence supports lower pump flows, the minimal safe flow rate during CPB has not been definitively established, and this value is likely influenced by the variables listed in Table 3.

The effect of pump flow rate on CBF and cerebral metabolism has been examined in several clinical trials. In general, most studies demonstrated that CBF remained relatively constant at pump flow rates of  $1.0\text{--}2.4\text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$  when hypothermic bypass was used,<sup>9,32,33</sup> Table 4. In contrast, Soma et al. observed that CBF increased proportionally to the CPB pump flow under conditions of moderate hypothermia.<sup>34</sup> Studies using animal models have also yielded conflicting results. These investigations have reported that variations in flow rate over a range typically used in adult CPB patients had no effect on CBF<sup>35,36</sup> or resulted in decreased CBF when flows were reduced.<sup>37,38</sup> The use of different methods of acid-base management and CBF measurement techniques might account for the differences in findings among investigators.

Systemic flow rates may impact perfusion of other organ systems besides the brain. Using laser Doppler flowmetry, Bastien et al. compared splanchnic perfusion during high ( $100\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and low ( $50\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) pump flows in rabbits.<sup>39</sup> Blood flow to the stomach, jejunum, and ileum was significantly reduced in the low flow group. In a swine model, reductions in pump flow did not affect CBF, but significantly reduced perfusion of all visceral organs.<sup>40</sup> Increasing the pump flow restored perfusion to the pancreas, colon, and kidneys, whereas restoration of systemic pressures with phenylephrine did not. Using a similar animal model, Mackay et al. reduced pump flows to achieve a systemic pressure of  $45\text{ mm Hg}$ .<sup>41</sup> Regional perfusion to the kidneys, gastrointestinal tract, and pancreas was significantly reduced at this flow. These studies suggest that blood flow to visceral organs may be compromised at lower pump flow rates.

The influence of systemic flow rate on outcomes after cardiac surgery has been poorly studied. Kolkka et al. reported a low incidence of neurologic and neuropsychiatric dysfunction (17.2%) in an observational study of 204 patients undergoing low-flow ( $30\text{--}50\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), low-pressure ( $30\text{--}60\text{ mm Hg}$ ) CPB.<sup>42</sup> Ellis et al. also observed a low incidence of neurocognitive dysfunction (17%) in 30 patients undergoing hypothermic ( $28^\circ\text{C}$ ) bypass at flow rates  $<40\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ .<sup>17</sup> Slogoff et al. examined the association between low flow on bypass ( $<1.6$

**Table 4.** Clinical Studies Examining the Effect of Pump Flow Rate on Cerebral Blood Flow and Metabolism

Study	No of Patients	Flow rate	Temperature	Acid-base management	MAP	Results (mm Hg)
Cook et al., 1997 <sup>32</sup>	30	1.2–2.3 L · min <sup>-1</sup> · m <sup>-2</sup>	27°C	α stat	50–70	No differences in mean CBF or CMR at high or low flows
Govier et al., 1984 <sup>9</sup>	67	1.0–2.2 L · min <sup>-1</sup> · m <sup>-2</sup>	27°C	α stat	45–70	No change in regional CBF or CMR at differing flow rates
Rogers et al., 1992 <sup>33</sup>	24	1.75–2.25 L · min <sup>-1</sup> · m <sup>-2</sup>	27°C	α stat and pH stat	68–75	No difference in CBF or CMR at differing flow rates
Soma et al., 1989 <sup>34</sup>	21	40–70 mL · kg <sup>-1</sup> · min <sup>-1</sup>	27°C	pH stat	59–70	CBF increased proportionally to flow rate

MAP = mean arterial blood pressures; CBF = cerebral blood flow; CMR = cerebral metabolic rate.

L · min<sup>-1</sup> · m<sup>-2</sup>) and adverse renal and neurologic outcomes in a prospective observational study.<sup>20</sup> Low flow during CPB was not a predictor of either adverse outcome. There is no evidence from large-scale randomized trials supporting a minimal safe flow rate during normothermic or hypothermic CPB. Furthermore, the optimal flow rate that supports the most favorable organ perfusion and results in improved clinical outcomes has not been determined.

### Hematocrit Values

Hemodilutional anemia is an inevitable consequence of CPB using asanguinous prime of circuits with conventional priming volumes. The degree of hemodilutional anemia that is observed on bypass is related to the patients' initial red cell mass (body size and hematocrit) and priming volume of the ECC. Potential advantages of hemodilution during CPB include reduced blood viscosity and improved microcirculatory flow, a reduced risk of hypertension during higher bypass flows, and a decreased requirement for intraoperative transfusions. Excessive hemodilution, however, may compromise DO<sub>2</sub> at the tissue level and contribute to hypotension during CPB. Although severe hemodilutional anemia may induce ischemic organ injury, transfusion of packed red blood cells (PRBCs) is not without risks and may be associated with increased morbidity and mortality in cardiac surgical patients.<sup>43–45</sup> A determination of optimal hematocrit on CPB requires an assessment of the risks and benefits of both hemodilutional anemia and transfusion of PRBCs.

A number of clinical investigations have examined the relationship between the severity of hemodilutional anemia (lowest hematocrit on bypass) and outcomes after cardiac surgery. Observational studies performed in the 1970s and 1980s suggested that patients tolerated hematocrit levels as low as 14%–18% on bypass without obvious adverse effects.<sup>46–49</sup> However, recent large databased investigations have described an association between lowest hematocrit on bypass and postoperative morbidity and mortality,<sup>50–59</sup> (Table 5). DeFoe et al. observed a

strong inverse relationship between hematocrit levels on bypass and in-hospital mortality, need for intra-aortic balloon pump support, and return to bypass after attempted separation.<sup>50</sup> In a cohort of 5000 cardiac surgical patients, Habib et al. also noted that early and late mortality, major morbidity, and resource utilization were significantly and systematically increased as hematocrit values decreased.<sup>51</sup> Both studies identified trends towards increased morbidity and mortality at all hematocrits below 22% to 23%.<sup>50,51</sup> Other large databased investigations have observed that lowest hematocrit on bypass was an independent risk factor for renal<sup>52–54</sup> and neurologic injury.<sup>57</sup> Karkouti et al. observed a 10% increased risk of stroke rate with each percent decrease in the nadir hematocrit,<sup>57</sup> (Fig. 1). Mathew et al. observed a higher incidence of neurocognitive decline in elderly patients randomized to receive profound hemodilution (hematocrit of 15%–18%).<sup>58</sup> The risk of developing acute renal failure or a significant increase in postoperative serum creatinine increased as hematocrit values decreased below 21%–24% on CPB.<sup>52,53,56</sup> It is conceivable that these data are contaminated by the fact that low hematocrit may simply be a surrogate for transfusion of PRBCs, and that it is the latter, rather than the former, that is the cause of the adverse outcomes.

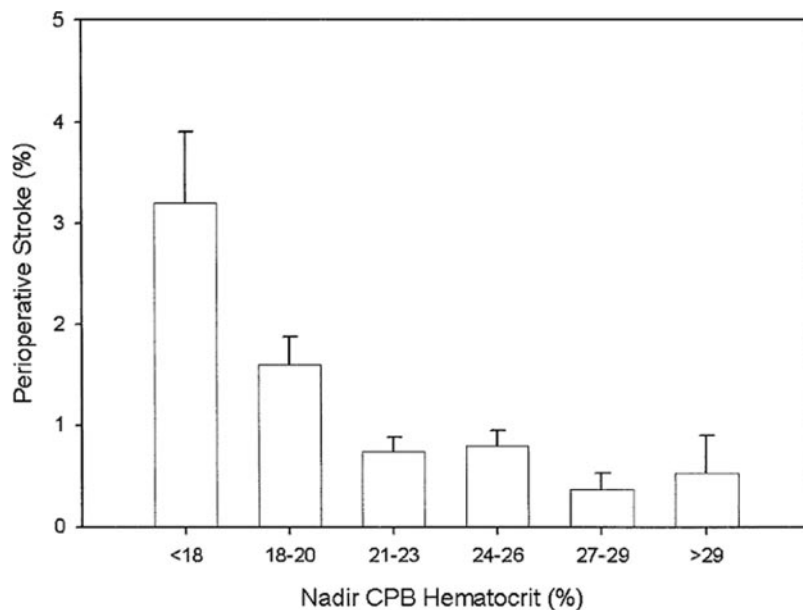
As previously noted, transfusion of PRBCs to increase hematocrit levels is not without risks. In addition to the well-known risks of allogeneic blood transfusion (transfusion reactions, transmission of infectious agents, immunosuppression), administration of PRBCs can markedly increase cytokine levels after CPB and enhance perioperative inflammation.<sup>59</sup> Databased investigations have demonstrated an association between blood transfusions and increased morbidity and mortality. Engoren et al. examined long-term survival data on 1915 primary CABG patients.<sup>43</sup> After correction for co-morbidities and other risk factors, transfusion was associated with a 70% increase in 5-yr mortality (risk ratio 1.7; 95% CI = 1.4–2.0; *P* = 0.001). In another retrospective analysis of 3024 patients undergoing CABG surgery, the effect of transfusion

**Table 5.** Lowest Hematocrit on CPB and Outcomes: Data-Based Investigations

Author	No of patients	Outcome variables	Critical Hct values	Results
DeFoe et al., 2001 <sup>50</sup>	6980	In-hospital mortality morbidity	23%	Lowest Hct associated with increased In-hospital mortality, need for IABP, and return to CPB
Habib et al., 2003 <sup>51</sup>	5000	In-hospital mortality morbidity long-term survival Resource utilization	22%	Lowest Hct associated with increased mortality, morbidity, and resource utilization
Fang et al., 1997 <sup>55</sup>	2738	In-hospital mortality	14% all patients 17% high-risk patients	Lowest Hct associated with increased mortality
Karkouti et al., 2005 <sup>52</sup>	9080	ARF requiring dialysis	<21% or >25%	Hct values <21% or >25% associated with increased risk of ARF
Habib et al., 2005 <sup>53</sup>	1760	Change in serum creatinine ARF	24%	Lowest Hct on CPB associated with increased risk of creatinine rise and ARF
Swaminathan et al., 2003 <sup>54</sup>	1404	Change in serum creatinine	None identified	Lowest Hct associated with creatinine rise
Ranucci et al., 2006 <sup>56</sup>	1766	In-hospital mortality morbidity	23%	Lowest Hct associated with cardiac low output syndrome and ARF
Karkouti et al., 2005 <sup>57</sup>	10,949	Stroke	None identified	Lowest Hct associated with increased risk of stroke

CPB = cardiopulmonary bypass; Hct = hematocrit; IABP = intraaortic balloon pump; ARF = acute renal failure.

**Figure 1.** The unadjusted relationship between lowest hematocrit on cardiopulmonary bypass (categorized into six groups) and risk of perioperative stroke. Reprinted with permission from Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeyesundera D, Ivanov J, Karski J. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *Ann Thorac Surg* 2005; 80:1381-7.



on 30-day and 1-yr mortality was determined.<sup>44</sup> After using a propensity scoring system to control for confounding variables, the adjusted hazard ratio for 1-yr mortality in transfused patients was 1.88 ( $P < 0.01$ ). Major postoperative morbidity may also be influenced by intraoperative transfusions. In a cardiac surgical patient population, transfusion of PRBCs has been associated with an increased risk of pneumonia,<sup>60,61</sup> mediastinitis,<sup>62</sup> and hospital length of stay.<sup>63</sup>

The findings from large databased studies have demonstrated that both severe hemodilution on CPB and transfusion of PRBCs increase the risk of adverse postoperative outcomes. The complex relationship between the two variables has been examined in two investigations. Both studies demonstrated that lowest

hematocrit on bypass was associated with postoperative renal dysfunction.<sup>53,56</sup> Paradoxically, transfusion of PRBCs on CPB aimed at reversing the deleterious effects of hemodilution significantly increased the risk of creatinine rise and renal failure. These results suggest that severe hemodilution may compromise  $DO_2$  at the tissue level and that transfusion of PRBCs does not improve, and may actually worsen, ischemic organ injury. Due to limitations inherent in databased studies, it is not possible to clearly declare a cause and effect relationship between either hemodilution or PRBC transfusion and adverse outcome, nor to define a safe threshold at which the benefits of transfusion of PRBCs outweigh the potential risks of hemodilution. Until such data are available, methods to limit the



degree of hemodilutional anemia should be aggressively applied to patients undergoing CPB. These techniques include delaying elective surgery in order to restore red cell mass to normal levels (iron, erythropoietin), limiting the volume of crystalloid administered pre- and post-CPB, reducing blood sampling in the perioperative period, the use of retrograde autologous priming of the CPB circuit, minimizing tubing size and length connecting the patient to the pump, and the use of miniaturized CPB circuits.

### Oxygen Delivery

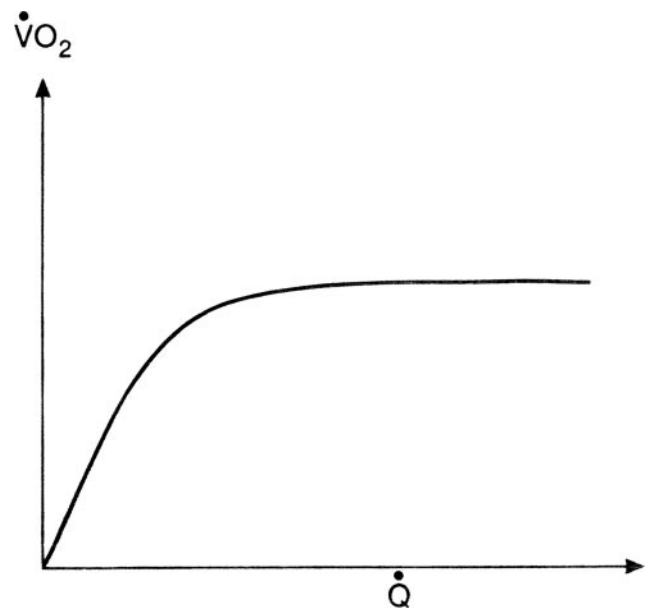
Systemic  $\text{DO}_2$  during CPB may be one of the most important determinants of "optimal" perfusion.  $\text{DO}_2$  is calculated by multiplying the pump flow rate by the arterial oxygen content:

$$\text{DO}_2 = \text{pump flow} \times ((\text{hemoglobin concentration} \times \text{hemoglobin saturation} \times 1.36) + (0.003 \times \text{arterial oxygen tension})).$$

The  $\text{DO}_2$  calculation incorporates two important perfusion variables that determine tissue oxygenation, hematocrit values, and pump flow rates into a single measure. In the clinical setting,  $\text{DO}_2$  can be improved by increasing pump flows, increasing hematocrit concentrations (transfusion of PRBCs or use of ultrafiltration for hemoconcentration), or by increasing hemoglobin saturation and the amount of dissolved oxygen (increasing the inspired oxygen concentration [ $\text{FIO}_2$ ]).

$\text{DO}_2$  values observed during CPB are typically less than those measured in awake and anesthetized subjects. In the pre-CPB period, the cardiac index is typically  $2.3$  to  $2.6 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . Assuming normoxia and a hemoglobin of  $12 \text{ g/dL}$ , this results in a  $\text{DO}_2$  of approximately  $350$ – $450 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ .<sup>64</sup> During CPB, if flows of  $2.2$  to  $2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  are maintained and hemoglobin values decrease to  $7$  to  $8 \text{ g/dL}$ ,  $\text{DO}_2$  will be reduced to  $200$ – $300 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . The reduction in  $\text{DO}_2$  that is observed on CPB is due primarily to a decrease in arterial oxygen content that occurs from hemodilution at the onset of bypass. If whole-body oxygen consumption ( $\text{VO}_2$ ) is unchanged, an increase in the oxygen extraction ratio is required to compensate for the reduced  $\text{DO}_2$ . Therefore, the safe margin between oxygen supply and demand may be narrowed during CPB.

The minimal safe  $\text{DO}_2$  during bypass, termed the critical  $\text{DO}_2$ , has been assessed in several investigations. As  $\text{DO}_2$  decreases,  $\text{VO}_2$  initially remains stable via increases in tissue oxygen extraction ("flow independent oxygen consumption"). At the point when maximal oxygen extraction is reached, whole body  $\text{VO}_2$  and tissue oxygenation begin to decrease and metabolic (lactic) acidosis begins to develop ("flow dependent oxygen consumption") (Fig. 2). The critical  $\text{DO}_2$  in anesthetized humans without CPB has been claimed to be approximately  $330 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ .<sup>65,66</sup>

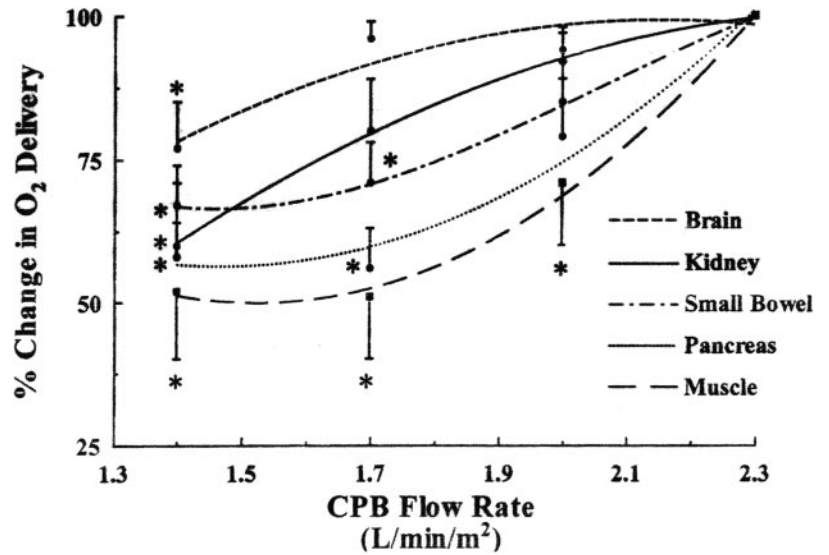


**Figure 2.** Relationship between oxygen delivery ( $\text{DO}_2$ ) and consumption ( $\text{VO}_2$ ). As flow ( $\text{Q}$ ) or  $\text{DO}_2$  decreases, oxygen extraction ratio increases and  $\text{VO}_2$  remains stable and independent of  $\text{DO}_2$ . At the knee of the curve, oxygen extraction is maximal, and flows below this critical  $\text{DO}_2$  value result in tissue hypoxia.

Critical  $\text{DO}_2$  values during CPB have not been definitively established. Studies in cardiac surgical patients have examined the relationship between  $\text{DO}_2$  and  $\text{VO}_2$ . Some investigations have identified a  $\text{DO}_2$  level below which  $\text{VO}_2$  values begin to decrease (critical  $\text{DO}_2$  of  $280$ – $300 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ).<sup>67,68</sup> In contrast, other investigators have observed a direct linear relationship between  $\text{DO}_2$  and  $\text{VO}_2$  during CPB, and have been unable to determine a critical  $\text{DO}_2$  value.<sup>69</sup>

The effects of alterations in pump flow,  $\text{FIO}_2$  and hematocrit concentrations on  $\text{DO}_2$  (and  $\text{VO}_2$ ) have been assessed in several investigations. In patients undergoing hypothermic CPB, reductions in pump flows to  $<1.2$ – $1.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  resulted in decreases in  $\text{VO}_2$ , suggesting that  $\text{DO}_2$  is compromised at flows below these values.<sup>70,71</sup> In contrast,  $\text{VO}_2$  was unchanged when  $\text{DO}_2$  was significantly decreased by reducing flow to as low as  $1.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ .<sup>72,73</sup> Increasing the  $\text{FIO}_2$  will improve  $\text{DO}_2$  during and after CPB. The influence of  $100\% \text{ FIO}_2$  on tissue oxygen tension is less certain, with studies in cardiac surgical patients demonstrating improved<sup>74</sup> and worsened<sup>75</sup> skeletal muscle oxygen tension during hyperoxia. Similarly, transfusion of PRBCs will increase systemic  $\text{DO}_2$ , yet may not improve oxygenation at the tissue level.<sup>74</sup> Changes that occur in stored blood, which include reductions in erythrocyte membrane deformability and  $2,3$  diphosphoglycerate levels, may account for the failure of transfusion to increase tissue oxygenation. The minimal hematocrit level that can support whole body  $\text{VO}_2$  and  $\text{DO}_2$  has not been established. In low-risk CABG patients, hemodilution to a hematocrit of  $20\%$  during normothermic bypass

**Figure 3.** Changes in regional oxygen delivery at varying bypass flow rates. Oxygen delivery to the brain and kidneys was relatively well maintained at flows more than  $1.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . However, oxygen delivery to muscle and visceral organs was significantly reduced at higher flow rates ( $1.7\text{--}2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ). Reprinted with permission from Boston US, Slater JM, Orszulak TA, Cook DJ. Hierarchy of regional oxygen delivery during cardiopulmonary bypass. *Ann Thorac Surg* 2001; 71: 260–4.



did not impair  $\text{DO}_2$  ( $\text{DO}_2$  was maintained above a “critical” value of  $330 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) or compromise clinical outcomes.<sup>76</sup> In a dog model of normothermic bypass,  $\text{DO}_2$  and  $\text{VO}_2$  were maintained at hematocrits between 39% and 25%.<sup>77</sup> Significant decreases in both values occurred when hematocrits were reduced to 18% or less.

The delivery of an acceptable whole-body  $\text{DO}_2$  does not ensure that  $\text{DO}_2$  to all organ beds is maintained. An organ-specific hierarchy of  $\text{DO}_2$  during CPB has been observed. During normothermic bypass in pigs,  $\text{DO}_2$  to the brain was maintained at baseline levels at pump flows of  $1.4$  to  $2.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  (Fig. 3). In contrast,  $\text{DO}_2$  significantly decreased to the kidneys, pancreas, and muscle beds at all flow rates studied (Fig. 3). These findings suggest that  $\text{DO}_2$  to the brain may be preserved at the expense of  $\text{DO}_2$  to other organ systems. In a similar animal model, significant decreases in mesenteric  $\text{DO}_2$  and progressive increases in mesenteric  $\text{VO}_2$  were observed during 120 min of normothermic bypass at  $100 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ .<sup>79</sup> A 21% decrease in splanchnic  $\text{DO}_2$  has been noted in patients during moderate hypothermic bypass at standard pump flows of  $2.1\text{--}2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ .<sup>80</sup> The use of higher pump flow rates ( $>2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) during normothermic bypass has been demonstrated to maintain splanchnic  $\text{DO}_2$  at baseline values.<sup>81</sup> In contrast, Sicsic et al. observed a 50% decrease in gastric mucosal red blood cell flow using laser Doppler flowmetry during hypothermic bypass even when the pump flow rate was increased ( $2.5\text{--}2.7 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) to maintain the  $\text{DO}_2$  at pre-CPB levels.<sup>82</sup>

Some insight about the impact of  $\text{DO}_2$  on outcomes may be derived from a prospective observational study examining the role of  $\text{DO}_2$  during bypass on postoperative renal dysfunction.<sup>83</sup> In a cohort of 1048 CABG patients, Ranucci et al. investigated the association between lowest  $\text{DO}_2$ , hematocrit, and pump flow on bypass and the development of postoperative

renal dysfunction.<sup>83</sup> The best predictor for acute renal failure and peak postoperative serum creatinine levels was the lowest  $\text{DO}_2$  on bypass, with a critical value of  $272 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . The authors concluded that targeting  $\text{DO}_2$  levels above a critical threshold is more important in preserving organ function than targeting specific hematocrit or pump flow values. Furthermore, their data demonstrate that organ injury can be prevented during more severe hemodilutional anemia by increasing pump flows and that pump flow should be adapted to hematocrit levels.

### Systemic Temperatures

By the late 1960s, hypothermia became a ubiquitous practice for adult patients undergoing CPB. Early experimental models demonstrated that hypothermia could reduce whole-body oxygen demands and increase ischemic tolerance of organ systems.<sup>84,85</sup> Although hypothermia effectively reduces overall  $\text{VO}_2$ , the balance between oxygen supply and demand can be impaired by reductions in tissue  $\text{DO}_2$  due to increased blood viscosity, reduced microcirculatory flow, and a leftward shift of the oxygen-hemoglobin dissociation curve. In the early 1990s, many cardiac centers began using systemic normothermia during CPB in conjunction with warm continuous cardioplegic techniques. Since that time, a large number of clinical trials have examined the impact of temperature management strategies on adverse outcomes after cardiac surgery.

The two largest randomized studies examining the effect of temperature management on neurologic outcomes reached conflicting conclusions. The Warm Heart Investigators group from Toronto noted no difference in the incidence of stroke at discharge in 1732 patients randomized to warm ( $33^\circ\text{--}37^\circ\text{C}$ ) or cold ( $25^\circ\text{--}30^\circ\text{C}$ ) bypass.<sup>86</sup> In contrast, investigators from Emory observed a significantly higher incidence of stroke and encephalopathy (4.5% vs 1.4%) in patients



randomized to normothermic ( $\geq 35^{\circ}\text{C}$ ) bypass compared to moderate hypothermic ( $\leq 28^{\circ}\text{C}$ ) bypass.<sup>87</sup> Differences in patient characteristics (higher risk patients in the Emory group), temperature management (higher systemic temperatures in the warm group at Emory), and cardioplegia composition and delivery may have accounted for the conflicting results between the two research groups. A meta-analysis of 19 randomized controlled trials assessing the effectiveness of hypothermia during CABG in reducing neurologic injury revealed nonsignificant trends towards a reduction in the incidence of nonfatal stroke in patients randomized to hypothermic bypass.<sup>88</sup>

The practice of systemic normothermia and continuous warm cardioplegia was introduced primarily to improve myocardial protection.<sup>87</sup> The incidence of perioperative MI has been reported to be reduced<sup>89,90</sup> or unaffected<sup>86,87,91,92</sup> by warm temperature management strategies. Similarly, investigators have observed that post-CPB low cardiac output syndromes occur less frequently in normothermic patients<sup>86,90</sup> or that the incidence of this complication is not influenced by temperature on bypass.<sup>87</sup> A lower incidence of cardiac arrhythmias has been reported when normothermic techniques are used.<sup>86,93,94</sup> However, patients undergoing normothermic bypass have lower systemic vascular resistances and require higher doses of vasoconstrictors perioperatively.<sup>93,95,96</sup>

The temperature maintained during CPB does not seem to affect renal or hematologic function. In a study of CABG patients randomized to warm, tepid, or hypothermic bypass, no differences were observed between the groups in creatinine clearance or release of sensitive markers of renal dysfunction.<sup>97</sup> A substudy of 300 patients randomized to warm or hypothermic bypass revealed no differences in postoperative creatinine clearance between groups.<sup>98</sup> In two small studies of warm versus hypothermic bypass, platelet function was significantly more impaired in patients randomized to hypothermia.<sup>99,100</sup> However, fibrinolytic activity may be greater at warmer temperatures.<sup>101</sup> Although hypothermia may impair the coagulation system, data do not clearly demonstrate that hypothermic patients have greater postoperative bleeding and transfusion requirements. A randomized trial with blood transfusion as a primary outcome variable observed no differences in blood loss or transfusion requirements between patients undergoing bypass at  $37^{\circ}\text{C}$  or  $25^{\circ}\text{C}$ .<sup>102</sup> Studies not specifically designed to examine hematologic outcomes have observed that bleeding and transfusions were higher in hypothermic groups<sup>89,92,103</sup> or not different between temperature groups.<sup>91</sup>

The majority of published randomized trials comparing warm versus cold temperature management during CPB have been insufficiently powered to detect differences in major morbidity and mortality. Combining clinical outcome data from smaller studies with meta-analysis may provide insight about less

frequent outcomes, such as death, stroke, or MI. A meta-analysis by Rees et al. examined the effectiveness of hypothermia in reducing neurologic and myocardial outcomes.<sup>88</sup> Nineteen studies were identified which met inclusion criteria. The pooled effect estimate documented a trend towards a reduction in the incidence of nonfatal stroke in the hypothermic group (OR 0.68 [0.43, 1.05]). In contrast, there was a trend towards a higher incidence of nonstroke related deaths in the hypothermic group (OR 1.46 [0.9, 2.37]). Although the incidence of low output syndrome was higher in the hypothermic patients, there was no difference between the groups in the occurrence of nonfatal MI. Pooling of all adverse outcomes revealed no clear advantages of either hypothermia or normothermia.

Current evidence does not support one temperature management strategy for all patients. As stated in a review, "the ideal temperature for CPB is probably an indeterminate value that varies with the physiologic goals."<sup>104</sup> Furthermore, the optimal rate and degree of rewarming have yet to be determined. Recent randomized investigations have demonstrated that slower rates of rewarming and lower temperatures at separation from bypass ( $34^{\circ}\text{C}$  versus  $37^{\circ}\text{C}$ ) were both associated with a reduced incidence of postoperative neurocognitive dysfunction.<sup>105–107</sup> Limiting arterial line temperature to  $37^{\circ}\text{C}$  may be useful in avoiding cerebral hyperthermia and injury, but has yet to be demonstrated in clinical trials. These findings suggest that aggressive rewarming practices may be contributing to neurologic injury in cardiac surgical patients.

### Pulsatile and Nonpulsatile Perfusion

The early mechanical pumps introduced into clinical practice in the 1950s delivered nonpulsatile flow. The lack of a suitable pump that would deliver physiological pulsatile flow led to the widespread application of nonpulsatile CPB. Technological advances in biomedical engineering that have occurred over the past 30 yr have allowed for the delivery of intermittent high-amplitude pressure and flow pulses during bypass. Proponents of pulsatile perfusion argue that pulsatile flow patterns improve major organ blood flow and augments  $\text{DO}_2$  at the tissue level. Others have concluded that pulsatile pumps increase the complexity of the CPB circuit and enhance the destruction of red blood cells and platelets. Despite five decades of intensive research, there is still vigorous debate about the benefits of pulsatile perfusion. More than 150 basic science and clinical investigations have been published which directly compared pulsatile and nonpulsatile perfusion.<sup>108</sup> Although there is an extensive body of literature, there remains uncertainty about the effects of pulsatile perfusion on clinical outcomes.

Table 6 lists some of the clinical studies that have examined the impact of pulsatile versus nonpulsatile

**Table 6.** Clinical Studies of the Effects of Pulsatile and Nonpulsatile Perfusion on Outcomes

	Improved with pulsatile flow	No difference between pulsatile and nonpulsatile flow
Mortality	Murkin JM et al., 1995 <sup>109</sup>	Taylor KM et al., 1982 <sup>110</sup>
Myocardial infraction	Murkin JM et al., 1995 <sup>109</sup>	Abramov D et al., 2003 <sup>111</sup>
Requirement for mechanical or pharmacologic circulatory support	Song Z et al., 1997 <sup>112</sup>	
Neurologic injury (stroke or neurocognitive dysfunction)	Taylor KM et al., 1982 <sup>110</sup>	Murkin JM et al., 1995 <sup>114</sup>
	Murkin JM et al., 1995 <sup>109</sup>	Henze T 1990 <sup>115</sup>
	Takahara Y et al., 2000 <sup>113</sup>	Abramov D et al., 2003 <sup>111</sup>
Renal injury		Badner NH et al., 1992 <sup>117</sup>
	Kocakulak M et al., 2005 <sup>116</sup>	
	Abramov D et al., 2003 <sup>111</sup>	
Splanchnic perfusion	Hamulu A et al., 1998 <sup>118</sup>	Mathie RT et al., 1997 <sup>120</sup>
	Gaer JA et al., 1994 <sup>119</sup>	
Inflammatory mediator release	Sezai A et al., 2005 <sup>121</sup>	Dapper F et al., 1992 <sup>123</sup>
	Driessen JJ et al., 1995 <sup>122</sup>	
Release of endogenous vasoactive mediators (catalcholamines, plasma renin)	Zamparelli R et al., 2000 <sup>124</sup>	Goto M et al., 1993 <sup>126</sup>
	Sezai A et al., 2005 <sup>121</sup>	
	Canivet JL et al., 1990 <sup>125</sup>	

perfusion on outcomes after cardiac surgery. No randomized trials that have been published have been adequately powered to definitively establish an effect of pulsatility on mortality. Prospective investigations enrolling 316–1820 patients have observed that in-hospital mortality is reduced<sup>109</sup> or unaffected<sup>110,111</sup> by pulsatile flow. Conflicting findings have also been reported about the effects of pulsatile flow on major organ dysfunction after cardiac surgery. Renal, cerebral, and gastrointestinal blood flow and function have been noted to be improved or unchanged when pulsatile pumps are used on CPB.<sup>112–120</sup> Similarly, clinical studies investigating the role of pulsatile versus nonpulsatile perfusion on the perioperative inflammatory or stress response have observed that humoral mediator release was attenuated or unaffected by the use of pulsatile pumps.<sup>121–126</sup> A recent evidence-based review of pulsatile CPB flow concluded that the data were conflicting or insufficient to support recommendations for or against pulsatile perfusion to reduce the incidence of mortality, MI, stroke, or renal failure.<sup>127</sup>

An assessment of the benefits and risks of pulsatile perfusion is complicated by important limitations in the experimental design in all published investigations. Most importantly, there is no precise and widely recognized definition of what constitutes and how to quantify pulsatile flow. Traditionally, pulse pressure is used to quantify pulsatility. However, the generation of a normal pulse pressure waveform does not ensure the delivery of a normal pulse flow waveform. Pulsatility should be defined in terms of hemodynamic energy levels since additional hydraulic energy is required to generate pulsatile flow and improve capillary perfusion.<sup>128,129</sup> Studies have demonstrated that with identical pulse pressures, the difference in terms of extra energy between two different pulsatile pumps may differ by more than 100%.<sup>130</sup> In addition,

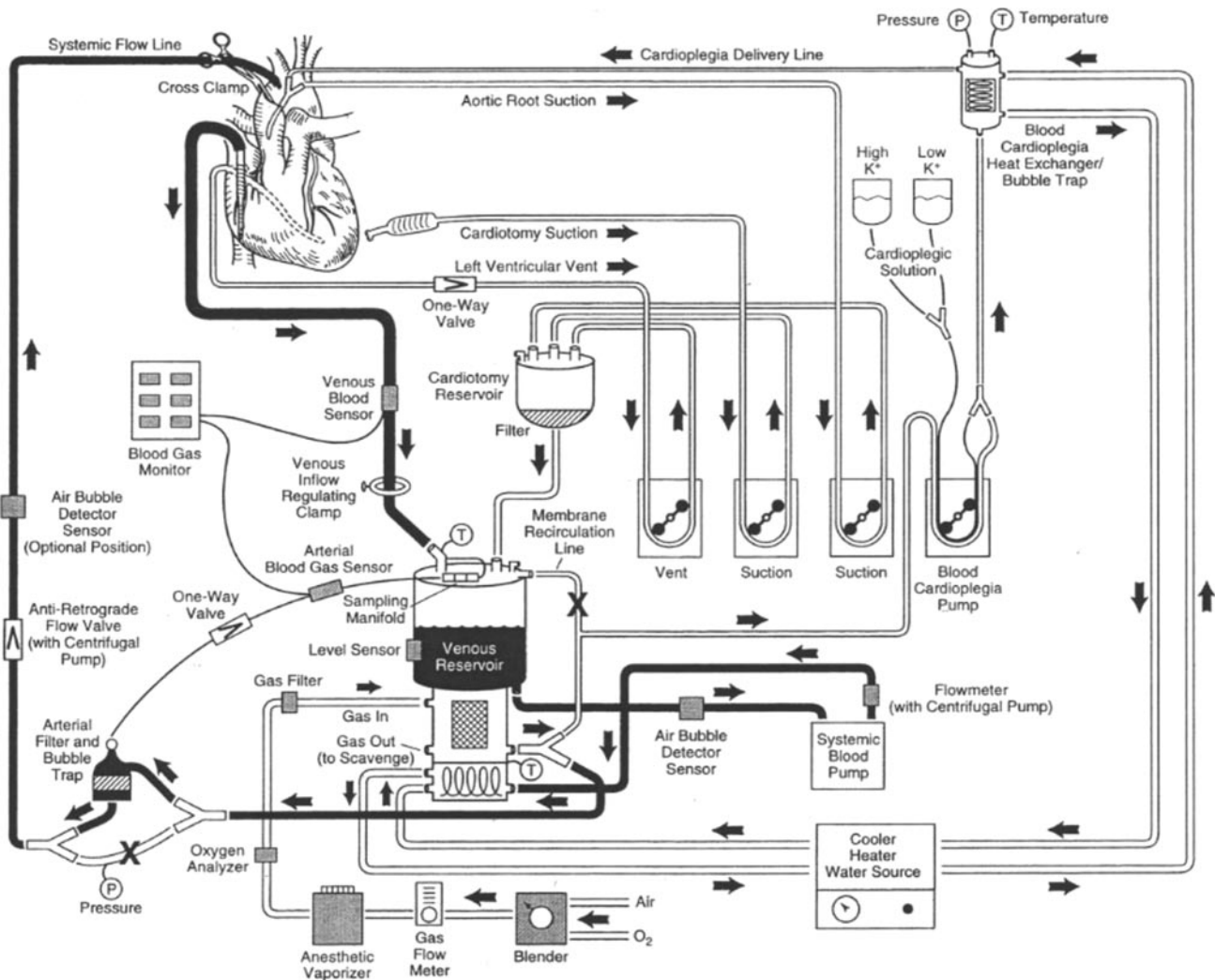
the hemodynamic energy delivered by currently approved pulsatile pumps is significantly less than normal physiologic pulsatility.<sup>131</sup> Transmission of the pressure-flow wave generated by the pulsatile pump can be affected by other CPB circuit components. A pressure decrease occurs as blood flows across the membrane oxygenator, and the type of oxygenator (hollow-fiber versus flat-sheet) can influence the quality of the pulsatility.<sup>132</sup> The design of the aortic cannula can also affect the pulsatile waveform morphology.<sup>133</sup> In order to clearly determine the benefits of pulsatile flow during CPB, future clinical investigators should attempt to quantify the energetics of the different perfusion modes, standardize the components of the CPB circuit (membrane oxygenator, arterial cannula) and carefully control the conduct of bypass.

#### pH and Paco<sub>2</sub> Management

The influence of acid-base management during CPB on outcomes has been recently reviewed in this journal.<sup>134</sup> Although basic science and clinical studies have demonstrated physiologic advantages to both  $\alpha$ -stat and pH-stat management under specific clinical scenarios, it is difficult to demonstrate clear benefits of either technique on clinical outcomes.

#### COMPONENTS OF THE CPB CIRCUIT AND OPTIMAL PERFUSION

The ECC is comprised of 11 distinct but related systems that provide the following functions: oxygenation, carbon dioxide removal, filtration, propulsion of blood, cooling and warming of blood, delivery of gases and volatile anesthetics to the “oxygenator,” temporary storage of blood from the heart and capacitance vessels, physiologic monitoring and safety systems with displays, alerts and alarms, a suction subsystem



**Figure 4.** Schematic diagram of typical cardiopulmonary bypass circuit displaying the components discussed in this review. Illustrated are the systemic blood pump (lower right), oxygenator and venous reservoir (incorporated as a single hard-shell unit which also includes the heat-exchanger, depicted in the lower center of this diagram), cardioplegia suction (upper center), and arterial line filter/bubble trap (lower left). Also displayed are multiple safety devices and monitors, cardioplegia delivery, field suction and vent systems, gas and water delivery systems for the oxygenator and heat-exchangers. Not displayed is the central data processing and monitoring console. (From Fig. 18.1 in Hensley FA, Martin DE, Gravlee GP. *A Practical Approach to Cardiac Anesthesia*, 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2008, with permission).

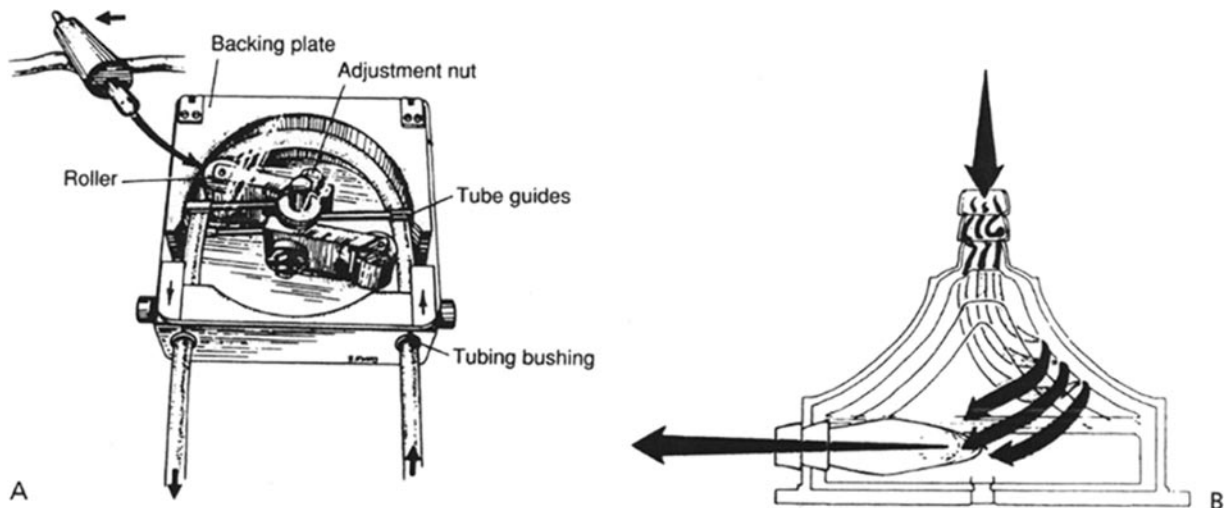
to salvage shed blood, sometimes ultrafiltration, and a cardioplegia delivery system to arrest, protect and reanimate the heart (Fig. 4). All of these systems function to support the circulation and to create an environment that allows the surgical team to safely operate on the heart and great vessels. The extracorporeal system consists of heart-lung console and disposable ECC components. The console serves as the platform from which these components function and includes pumps, vacuum sources, a variety of sensors and monitoring devices, and a central microprocessor that is essential for the optimal management of the extracorporeal system. Microprocessor technology enables communication between components and the acquisition of data from the heart lung machine and monitoring devices used during surgery. This technology improves the operator's ability to monitor and react to multiple complex signals.

Modern heart-lung machines are equipped with multilevel safety systems and microprocessors that may control and monitor individual components, including alerts and alarm systems and servo-regulation. Monitoring and safety components protect the patient and also foster more precise control of physiological variables. Although a minority of all cardiac programs currently use all of these systems, there is a general consensus among clinicians that this technology optimizes safety and performance and will soon be a standard of care.

**Optimal Blood Pump**

Tayama et al. suggested that the ideal blood pump for extracorporeal circulation must have the capacity to deliver up to 7 L per minute against a pressure of 500 mm Hg, should not damage the cellular or acellular components of the blood, should have smooth





**Figure 5.** Arterial Blood Pumps: (A) Roller Pump-Plastic (“pump head”) tubing rests inside the race-way. The rollers mounted on arms 180 degrees apart nearly occlude the tubing and act like a rolling pin, squeezing the blood ahead of it and out the pump. It is insensitive to afterload. (B) Centrifugal pump (From Fig. 12.6 in Estafanous FG, Barash PG, Reves JG. *Cardiac Anesthesia. Principles and Clinical Practice*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission).

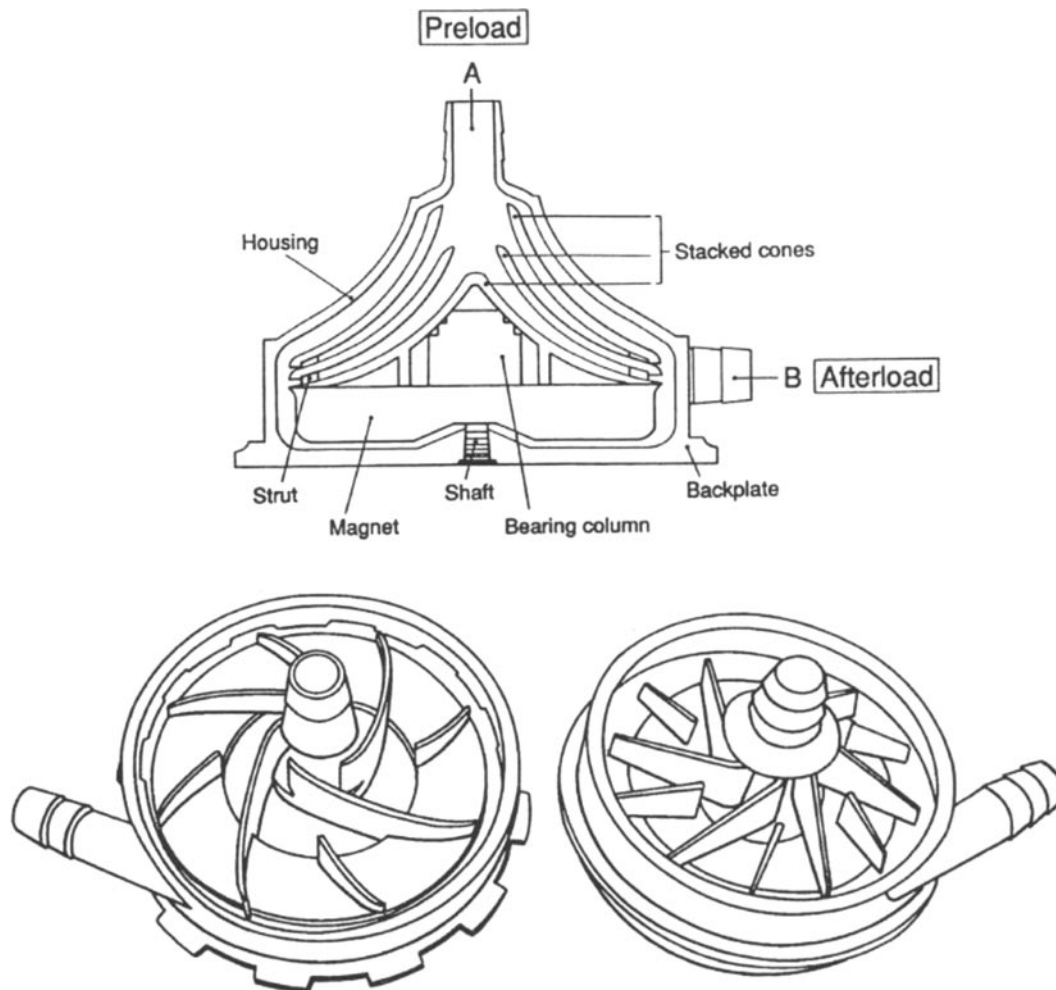
surfaces, must be free of areas of stasis or turbulence, should have accurate and reproducible flow measurement, and should have a back-up or manual mode of operation where a motor or power failure occur.<sup>135</sup> With roller pumps, the propulsion of blood occurs by the action of two rollers sequentially compressing a segment of tubing causing the forward movement of blood (Fig. 5). The magnitude of hemolysis is related to both the time and exposure of the blood to shear forces generated by the pump. A region of high pressure and shear force is created at the leading edge of the roller where the tubing is compressed, which is followed by period of negative pressure as the tubing expands behind the roller. This momentary negative pressure under certain conditions may induce the cavitation of air dissolved in the solution. Furthermore, particulate emboli may be generated by micro fragmentation (or spallation) of the inner surface of the tubing where the roller contacts the tubing and where the fold at the edges of the tubing occurs.<sup>136</sup> Studies of tubing wear over time have shown that polyvinylchloride fragments generated from roller pumps are numerous, frequently  $<20\ \mu\text{m}$  in diameter, and begin to occur during the first hour of use.<sup>137</sup>

Centrifugal pumps are nonocclusive pumps that function by producing a constrained vortex within a polycarbonate structure that results in the forward movement of fluid (Figs. 5, 6). The rate of flow is dependent on preload from the blood reservoir or blood source and afterload produced by downstream resistance. Blood flow rate is increased by increasing the revolutions per minute of the cone suspended within the polycarbonate housing. The cones or impeller are coupled with a motor drive by magnets. There have been reports of thrombus formation when these pumps are used with low anticoagulation or for prolonged periods of time.<sup>138</sup> Improved designs have

addressed issues of stasis, heat generation, and bearing wear.

A number of investigators have performed *in vitro* studies comparing centrifugal pumps and roller pumps in terms of blood handling during short- and long-term use.<sup>139–148</sup> Several studies reported less hemolysis with the centrifugal pump when tested *in vitro*.<sup>139–142</sup> Tamari et al. examined hemolysis under various flow and pressure conditions in an *in vitro* model using porcine blood and concluded that the hemolysis index was related to the duration of blood exposure to shear, the ratio of pump pressure difference between the inflow and outflow and the flow rate of the pump.<sup>144</sup> Rawn et al. compared an under-occlusive roller pump to a centrifugal pump and found a significantly higher index of hemolysis in the centrifugal pump (3.38–14.65 vs 29.58 gm/100 L pumped).<sup>145</sup> How relevant these often very long-term (24 h or longer) *in vitro* studies are to relatively short-term ( $<6$  h) CPB used for supporting cardiac surgery is not clear.

A number of clinical trials have been conducted to compare centrifugal and roller pumps in relation to emboli generation, blood trauma, and clinical outcomes,<sup>149–170</sup> (see Web-based supplementary material for details of clinical investigations). In a trial by Wheeldon et al., significantly less microemboli generation, less complement activation, and better preservation of platelet count was observed in patients randomized to the centrifugal pump.<sup>149</sup> A similar improvement in platelet preservation in the centrifugal group was observed in a retrospect review of 785 cases, particularly with bypass times of more than 2 h.<sup>150</sup> Rates of hemolysis have been compared in seven randomized clinical trials. Two reported greater hemolysis with roller pumps,<sup>161,168</sup> one observed greater evidence of hemolysis with a centrifugal



**Figure 6.** Centrifugal Blood Pump: (A) plastic cone(s) or impeller is mounted inside the conical plastic housing. The impeller is rotated by the motor outside and beneath the base of the plastic housing (magnetic coupling). The difference of the velocity (centimeters per second) of the narrow portion of the impeller cone (at the top) as compared with the wider portion of the cone (at the bottom) creates a pressure differential which drives the blood through the pump. It is sensitive to afterload. (From Fig. 18.3 in Hensley FA, Martin DE, Gravlee GP. *A Practical Approach to Cardiac Anesthesia*, 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2008, with permission).

pump,<sup>149</sup> and four found no difference between the two types of pumps.<sup>151,152,163,167</sup> A retrospective analysis of data from 3438 consecutive patients revealed that the use of the centrifugal pump was associated with a risk reduction for adverse neurologic events of 23% to 84%.<sup>157</sup> Randomized trials with neurologic measures as a primary outcome variable, however, have not demonstrated significant differences in neuropsychologic outcomes or S100  $\beta$  levels between types of pump.<sup>153,155</sup> In the largest randomized trial, Klein et al. assigned 1000 adult cardiac patients to management with a roller pump or a centrifugal pump.<sup>152</sup> Although differences in mortality between groups was not observed, clinical benefits in blood loss, renal function, and neurological outcome were demonstrated in the centrifugal group. Most of the recent studies that examined centrifugal pumps also incorporated other variables in the study design that could impact outcomes, including surface coating and reservoir design (open versus closed).<sup>160–163</sup> Although the majority of the randomized trials show benefit to

systems designed with centrifugal pumps, it is difficult to determine the influence of these other variables (such as lower prime volume, surface coating, more limited surface area, or reduced air to blood contact) on clinical outcomes.

According to the recently published guidelines by the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists, it is not unreasonable to select a centrifugal pump rather than a roller pump, but primarily for safety reasons rather than blood conservation (Class IIb, Level of Evidence B).<sup>171</sup> In 2000, approximately 50% of the cardiac centers in the United States routinely used centrifugal pumps.<sup>172</sup>

#### Optimal Surface Coating

Surfaces coatings play a role in pacification of the interface between the blood and the circuit components. Although not definitively proven, attenuation of the inflammatory and coagulation pathways should

translate into decreased postoperative morbidity directly related to platelet dysfunction, bleeding complications, and end organ damage. The desire to avoid anticoagulation of patients undergoing extensive thoracic aortic surgery led to the first reported use of a shunt with a graphite- Benzalkonium-heparin coating.<sup>173</sup> The use of heparin coating of the CPB circuit was first introduced with the intent of supplanting systemic anticoagulation with heparin. Subsequently, this concept of eliminating heparin was abandoned and replaced with a strategy of using a lower heparin dose and tolerance of a lower activated clotting time with a heparin coated CPB circuit.<sup>174–178</sup> *In vitro* and *in vivo* studies of these surfaces demonstrated reductions in coagulation and systemic inflammatory processes. Numerous clinical studies have compared the effectiveness of heparin-treated surfaces with circuits without heparin coatings.<sup>179–204</sup> Most investigations have shown evidence of reduced platelet activation,<sup>183–186</sup> attenuation of inflammatory processes,<sup>187–194</sup> and improvement in clinical outcomes (bleeding and transfusions,<sup>195–197</sup> pulmonary function,<sup>198,199</sup> and cognitive outcomes<sup>200–202</sup>).

Unfortunately, most of the studies are small and differ substantially in regards to anticoagulation management with heparin, the use of a partially coated or completely coated circuit, the method by which cardiomy blood was managed, type of heparin coating, and variations in measured end-points. The heterogeneity of the randomized trials related to heparin coatings confounds the use of meta-analysis as a method of summarizing the effectiveness of these circuits.<sup>171,179</sup> Stammers et al. used weighted means in an effort to summarize the effects of 27 randomized controlled trials of heparin-coated circuits that included 1515 patients.<sup>179</sup> They concluded that heparin-coated circuits, when compared to similar noncoated circuits, resulted in decreased hospital costs, shorter intensive care unit length of stay, and reduced bleeding-related complications. Furthermore, immunological factors were maintained better with the use of the Carmeda-coated circuits and hematological factors, excluding platelet count, favored the Duraflo II heparin coating. The most recent meta-analysis comparing heparin-coated circuits to uncoated circuits was published in 2007.<sup>205</sup> Their analysis indicated that the heparin-bonded circuits significantly decreased the incidence of blood transfusion, re-sternotomy, duration of ventilation, and hospital length of stay, but had no effects on the other adverse events evaluated. The authors concluded that heparin-coated circuits seem to confer a benefit to patients. However, they noted the lack of published research in high-risk patients, in which clinically relevant end-points such as death and stroke would be more prevalent.

Recent guidelines conclude that “heparin-coated bypass circuits (oxygenator alone or the entire circuit) are not unreasonable for blood conservation (Class IIb-Level of Evidence B)<sup>171</sup>” and that “reduction of

circuit surface and the use of biocompatible surface-modified circuits might be useful–effective in reducing the systemic inflammatory response (Class IIa-Level of Evidence B).<sup>206</sup>”

### Optimal Oxygenator

The introduction of hollow-fiber membrane oxygenators in 1980 was a major step forward for CPB. The first hollow-fiber oxygenators used designs with blood flowing through the fiber with the gas compartment surrounding the fibers. All of the recently available oxygenators are of a configuration with blood flow surrounding the fibers with gas flow directed through the hollow fibers (Fig. 7). Oxygenator gas transfer performance is governed by characteristics of the membrane compartment. For example, a decrease in fiber diameter results in an increase in gas transfer, a decrease in prime volume, an increase in pressure drop, an increase in shear, and an increase in platelet activation.<sup>207</sup>

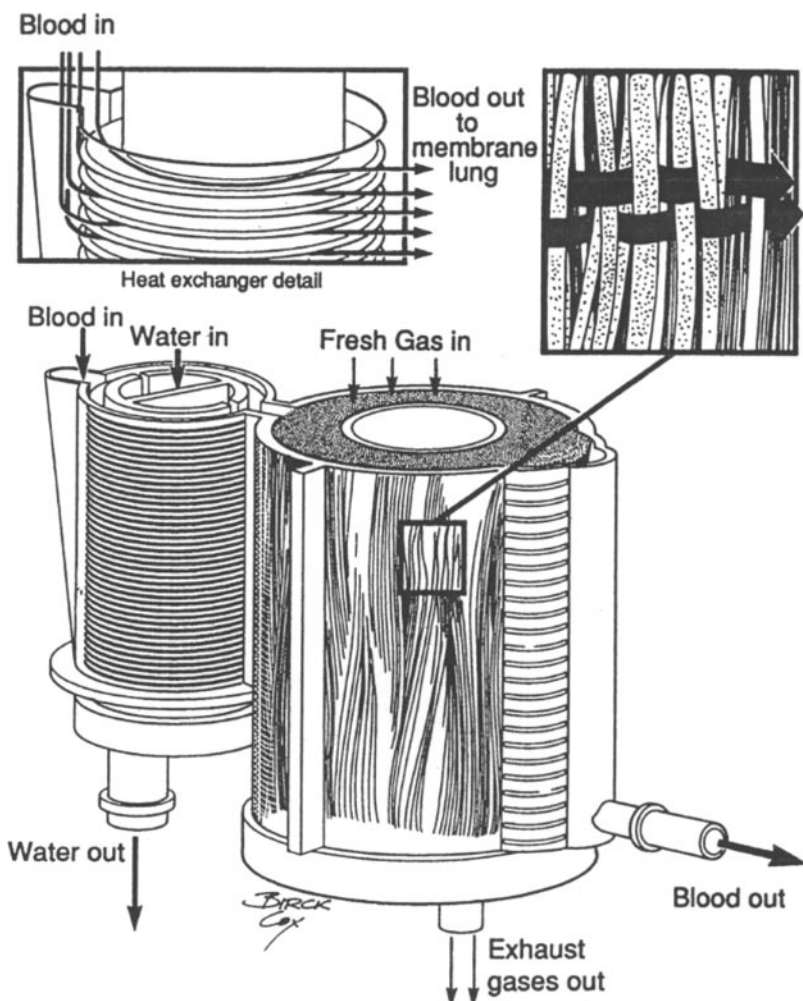
Numerous studies have identified the occurrence of gaseous microemboli (GME) during cardiac surgery with CPB.<sup>208–211</sup> Investigations that have examined the air-handling capabilities of oxygenators have demonstrated that all of the currently available oxygenators do not sufficiently remove GME when challenged with air in the inflow.<sup>212–214</sup> In addition, commonly used microporous membrane oxygenators have widely variable characteristics related to how they handle gas.<sup>212,213</sup> Design characteristics of some of these devices allow them to partially remove GME, as well as impact the size and numbers of microbubbles.

### Optimal Reservoirs

There are two general categories for venous reservoirs, open (“hard shell”) and closed (“collapsible bag”) systems. Open systems have a hard polycarbonate venous reservoir and usually incorporate a cardiomy reservoir and defoaming compartment. Closed systems are collapsible polyvinyl chloride bags that have a minimal surface area and often a thin single-layer screen filter. These systems do not have an integrated cardiomy reservoir and addition of a separate reservoir is required if cardiomy suction is to be used. In order to allow passive removal of air, filters and defoaming compartments are incorporated into the venous reservoir and air-trapping ports are placed at the highest level of the blood flow path within the oxygenator. The use of an open system offers several distinct advantages. Unlike collapsible reservoirs, it is not necessary to actively aspirate air, which may be entrained in the venous line during CPB. Large air bubbles migrate to the top of the reservoir and escape through strategically placed vents on the reservoir cover. An additional benefit of the use of “open” hard shell reservoir systems is the capability of applying vacuum-assisted venous drainage.

The prime volume may be slightly reduced by use of an open venous reservoir. With open systems,





**Figure 7.** Hollow fiber microporous membrane oxygenator. The oxygenator contains multiple bundles of hollow fibers. “Ventilating” gas (oxygen, air, volatile anesthetic agents,  $\pm$  carbon dioxide) is passed through the inside of the hollow fibers, while the venous return blood is passed around the hollow fibers to accomplish gas exchange by diffusion. Turbulence of the blood as it passes around the fibers assures effective gas exchange with all of the blood. (From Fig. 18.4 in Hensley FA, Martin DE, Gravlee GP. *A Practical Approach to Cardiac Anesthesia*, 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2008, with permission).

however, the circulating blood is exposed to a larger and more complex surface that contains defoaming sponges and antifoam agents. Furthermore, with use of an open system air entrained in the venous line is likely to be ignored since it is not necessary to actively purge the air as required with use of the closed system. Thousands of GME can be introduced into the patient’s arterial circulation if air becomes continuously entrained into the venous inflow, a condition that would not be overlooked or easily tolerated with a collapsible reservoir.

Recently, several randomized clinical trials have demonstrated superior clinical outcomes with systems equipped with a closed reservoir and a centrifugal arterial pump (Table 7). Less complement activation and release of polymorphonuclear elastase has been observed with the use of a closed system.<sup>169</sup> Schönberger et al. prospectively studied differences in inflammatory and coagulation activation of blood in cardiac patients treated with open and closed reservoir systems.<sup>215</sup> Levels of complement 3a, thromboxane B2, fibrin degradation products, and elastase were significantly higher in open reservoir patients during bypass. Furthermore, the largest amount of shed blood loss and the greatest need for colloid-crystalloid

infusion was observed in the patients supported with open reservoir systems.

The advantages of the open system are largely related to ease of use. Some of the disadvantages of open systems may be attenuated by systematically adopting good techniques (eliminating the entrainment of air in the venous line should it occur, careful use of the cardiotomy suction system, maintaining a safe operating level in the venous reservoir, and use of a level detector on the venous reservoir). However, cardiac surgery teams need to be well aware that the use of open systems with integrated cardiotomy suction renders the patient vulnerable to the unintended consequences of gaseous and lipid emboli. Vigilance is necessary to protect the patient undergoing cardiac surgery. The STS/SCA guidelines state that it is not unreasonable to use an open venous reservoir system for reduction in blood utilization and improved safety (Class IIb-Level of Evidence C).<sup>171</sup>

### Cardiotomy Suction

It is now known that cardiotomy suction blood contains fat, bone, lipids, and other debris from the surgical field that may exacerbate the systemic inflammatory response and microcirculatory dysfunction.

**Table 7.** Clinical Studies Comparing Open Venous Reservoirs, Cardiomy Suction vs Closed Venous Reservoirs

Author (ref)	Study design	Patients each group	Comparative groups	Surgery	Outcome measure	Result
Jensen et al., 2003 <sup>169</sup>	RCT	20	NHC, RP, OR vs HC, CP, CS	Peds <10 kg	Complement PMN elastase TNF alpha IL-6 IL-8	Combined System Lower in HC, CR, CP Lower in HC, CR, CP NS NS NS
Schonberger et al., 1995 <sup>215</sup>	RCT	10	OR with CARD vs CR		Hemolysis Shed blood Loss Colloid Infusion RBC transfusions	Favored CR <i>P</i> < 0.05 Favored CR <i>P</i> < 0.05 NS Favors CS but NS
Aldea et al., 2002 <sup>220</sup>	RCT	12	Group 1 = NCARD NHC Group 2 = HC CARD Group 3 = HC NCARD	Adult CABG	Thrombin generation PMN elastase levels beta-Thromboglobulin Neuron-specific enolase	Group 1 > Group 2 > Group 3 Group 1 > Group 2 > Group 3 Group 1 > Group 2 > Group 3 Group 1 > Group 2 > Group 3
Lindholm et al., 2004 <sup>160</sup>	RCT	20	CP, CR, HC, CARD vs RP, OR, NHC, CARD	CABG or AVR  Elderly adults	Complement PMN elastase  TNF IL-6 IL-8 Bb (compliment fragment)	Lower in HC, CR, CP warming + 1 hr post CPB Lower in HC, CR, CP warming + 1 hours post CPB  Lower in HC, CR, CP at rewarm Lower in HC, CR, CP at rewarm Lower in HC, CR, CP
Nuttall et al., 2006 <sup>221</sup>	RCT	15	2 × 2 factorial groups Cardiotomy suction vs cell saver HC vs NHC	Adult CABG	Platelet function (PF)  (PF 5 min. Before Separation)  All other platelet function Transfusion	NS  Favored HC CR  NS NS
Jewell et al., 2003 <sup>218</sup>	RCT	10	Cardiotomy suction vs cell saver	Adult CABG	Fat content reduction in blood  Transfusion Blood loss	Favored cell saver (87% reduced versus 45%)  NS NS
Brooker et al., 1998 <sup>219</sup>	RCT	13	Group I = right-heart CPB <i>n</i> = 3 Group II ( <i>n</i> = 2), lower-extremity CPB <i>n</i> = 2 Group III hypothermic CPB <i>n</i> = 3 Group IV hypothermic CPB with Cardiomy suction <i>n</i> = 5	Dogs	Small Capillary Arterial Dilations (SCADS)	SCADS in Group IV <i>P</i> < .04

RCT = Randomized controlled trial; HC = heparin-coated; NHC = not heparin-coated; RP = roller pump; CP = centrifugal pump; OR = open reservoir; CR = closed reservoir; CS = cardiomy suction; CARD = cardiomy suction system; NCARD = no cardiomy suction system; NS = not significant; Peds = Pediatric; CABG = coronary artery bypass grafts; PMN = polymorphonucleocytes; SCADS = small capillary arterial dilations; TNF = tumor necrosis factor; IL = interleukin; AVR = aortic valve replacement; CPB = cardiopulmonary bypass.

These substances may traverse the CPB circuit, enter into the arterial line, and ultimately obstruct the microcapillary circulation of the patient. Brown et al. identified thousands of embolic lesions in the brains of patients who died within 3 wk of cardiac surgery and reported an association between embolic lesions and duration of CPB.<sup>216</sup> For each 1-h increase in the duration of CPB, the embolic load increased by 90.5%. Cardiomy suction blood has been identified as a major source of lipid emboli in several studies.<sup>217–219</sup>

For this reason, some have advocated eliminating the use of cardiomy suction which is returned directly to the ECC. Several clinical studies have examined the effects of eliminating cardiomy suction (Table 7). In a randomized trial enrolling CABG patients, use of cardiomy suction resulted in significant increases in thrombin generation, neutrophil and platelet activation, as well as the release of neuron-specific enolase.<sup>220</sup> Nuttall et al., in a study of patients in whom an open venous reservoir was used, compared the return of cardiomy suction directly to the ECC, versus sequestration and processing of cardiomy blood to a cell saver.<sup>221</sup> A battery of blood tests were performed to evaluate platelet function. No significant difference in any of the tests or in blood transfusion requirements was observed. A recent randomized trial of 266 patients undergoing predominantly CABG surgery compared return of unprocessed cardiomy suction blood (control group) to that processed by centrifugal cell washing followed by lipid filtration (treatment group).<sup>222</sup> Greater blood product administration and blood loss were observed in the treatment group. No differences in microemboli generation, neurocognitive dysfunction, or other adverse events were demonstrated between groups. Further studies are needed to define the impact of cardiomy suction on clinical outcomes.

### Arterial Line Filters

Arterial line filters significantly reduce the load of gaseous and particulate emboli and should be used in CPB circuits.<sup>223,224</sup> Some studies suggest that 20- $\mu$ m filtration is superior to 40- $\mu$ m filtration in the reduction of cerebral embolic counts.<sup>224</sup> A dose-response relationship between GME and subtle neurological injury has been reported, and some studies have demonstrated a protective effect of arterial line filtration on neurologic outcomes.<sup>225–227</sup> A clinical trial by Whitaker et al. showed that the use of a leukocyte-depleting arterial line filter reduced cerebral embolic count and demonstrated a trend (not statistically significant) towards improved postoperative psychometric test scores.<sup>228</sup> The GME separation performance of 10 different arterial line filters in clinical use has been recently evaluated.<sup>229</sup> All were found to be moderately effective, and rated pore size did not predict performance. A systematic review of the data related to arterial line filtration reported that the level

**Table 8.** Recommendation for the Practice of Cardiopulmonary Bypass by Shann et al., 2006<sup>206</sup>

1. The clinical team should manage adult patients undergoing moderate hypothermic CPB with alpha stat pH management (Class I, Level A)
2. Limiting arterial line temperature to 37°C might be useful for avoiding cerebral hyperthermia (Class II a, Level B)
3. Direct reinfusion to the CPB circuit of unprocessed blood exposed to pericardial and mediastinal surfaces should be avoided (Class I, level B)
4. Blood cell processing and secondary filtration can be considered to decrease the deleterious effects of reinfused shed blood (Class IIb, level B)
5. In patients undergoing CPB at increase risk of advance neurologic events strong consideration should be given to intraoperative TEE or epiaortic ultrasonographic scanning of the aorta: (1) to detect nonpalpable plague (class I, level B) and (2) for reduction of cerebral emboli (Class II a, Level B)
6. Arterial line filters should be incorporated in the CPB current to minimize embolic load delivered to the patient (Class I, Level A)
7. The clinical team should maintain perioperative blood glucose concentrations within an institution's normal clinical range in all patients, including non-diabetic subjects (Class I, Level B)
8. Efforts should be made to reduce hemodilution, including reduction of prime volume, to avoid subsequent allogeneic blood transfusion (Class I, Level A)
9. 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 II a, Level B)

of evidence supporting this practice was high (Class I-Level of Evidence A).<sup>206</sup>

### EXPERT OPINIONS AND CONSENSUS GUIDELINES: OPTIMAL PERFUSION DURING CPB

Consensus statements are one way of processing, integrating, summarizing and interpreting evidence to assist with applying the data to clinical practice. Although based upon various levels of evidence, the process of developing such guidelines and consensus statements, by design, accepts, if not encourages, bias on the part of the "experts" (i.e., the members of the consensus panel) in selecting which evidence to use, and in weighing its value. Thus the final document is the product of a combination of "eminence" and "evidence", and the reliability is highly dependent on the quality of the panel of experts.<sup>230</sup> At least three such documents have been recently published which relate to CPB<sup>134,171,206</sup> Hogue et al. provided an evidenced-based appraisal of current practice of CPB on neurologic outcome which was recently published in this journal<sup>134</sup> Shann et al. provided another evidence-based review of the practice of CPB as it relates to neurologic injury, glycemic control, hemodilution, and the inflammatory response.<sup>206</sup> (summarized in Table 8) Finally, the STS and the Society of Cardiovascular Anesthesiologist have produced a



**Table 9.** Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists (STS/SCA) Blood Conservation Guidelines (Ferraris et al., 2007)<sup>171</sup>

1. During cardiopulmonary bypass with moderate hypothermia, transfusion of red cells for a hemoglobin  $\leq 6$  gm/dL is reasonable except in patients at risk for decreased cerebral oxygen delivery (i.e. history of CVA, diabetes, cerebrovascular disease, carotid stenosis) where higher hemoglobin levels may be justified. (Class IIa, Level C)
2. In the setting of hemoglobin values exceeding 6gm/dl while on CPB, it is reasonable to transfuse red cells based on the patient's clinical situation and this should be considered as the most important component of the decision making process. Indications for transfusion of red blood cells in this setting are multifactorial and should be guided by patient-related factors (i.e. age, severity of illness, cardiac function, or risk for critical end organ ischemia), the clinical setting (massive or active blood loss), and laboratory or clinical parameters (e.g. hematocrit, SVO<sub>2</sub>, ECG or echocardiographic evidence of myocardial ischemia etc.). (Class IIa, Level C)
3. In patients on CPB with risk for critical end-organ ischemia/injury, it is not unreasonable to keep the hemoglobin  $\geq 7$  gm/dL. (Class IIb, Level C)
4. It is not unreasonable to use open venous reservoir membrane oxygenator systems during cardiopulmonary bypass for reduction in blood utilization and improved safety. (Class IIb, Level C)
5. All commercially available blood pumps provide acceptable blood conservation during CPB. It is not unreasonable to prefer centrifugal pumps because of perfusion safety features. (Class IIb, Level B)
6. Heparin coated bypass circuits (either the oxygenator alone or at the entire circuit) are not unreasonable for blood conservation in cardiac operations. (Class IIb, Level B)
7. It is not unreasonable to use low prime and minimized extracorporeal bypass circuits to reduce the fall in hematocrit during CPB as part of a multimodality blood conservation program. (Class IIb, Level B)
8. Retrograde autologous priming of the CPB circuit is not unreasonable for blood conservation. (Class IIb, Level B)

document on perioperative blood transfusion and blood conservation in cardiac surgery as part of their Practice Guidelines Series.<sup>171</sup> In Table 9 we have summarized the conclusions in that document which relate to this review.

## CONCLUSIONS

The vast majority of patients survive cardiac surgery using contemporary techniques of CPB with little evidence of serious harm. Thus it may be more appropriate to identify patients at higher risk of adverse outcome and concentrate our efforts to optimize CPB for these patients. Another productive strategy is to attempt to identify patients who are not tolerating CPB at that time and intervene immediately.

There are currently limited data upon which to confidently make strong recommendations regarding how to conduct optimal CPB. The current attempts to synthesize the published literature through the development of evidence-based guidelines are helpful but

of uncertain reliability. It is incumbent upon centers to be knowledgeable about the published evidence and to critically assess their own practice to determine the extent to which their practice is consistent with the guidelines. Finally, changes should be initiated in areas where there is divergence. When changes are initiated, outcomes should be scrutinized to determine if the change resulted in the intended effect.

There is a critical need for high quality studies (i.e., large, well conducted, randomized controlled trials), particularly addressing high-risk patient groups. Furthermore, such studies must precisely define the components of the CPB circuit and the conduct of (techniques of) CPB. Many published studies only state that "standard CPB techniques were used" leaving the reader to wonder if the findings may be generalized. The same level of scrutiny and scientific analysis should be applied to new developments in CPB technology and techniques as are given to new drugs. However, continuing traditional practices which are not supported by high-level evidence is equally inappropriate. We need to critically appraise all aspects of the practice of CPB, and when found not to be based on solid evidence, we should seek evidence by appropriately designed and powered scientific studies assessing clinically significant outcomes.

## REFERENCES

1. Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. *Minn Med* 1954;37:171-85
2. Kirklin JW, DuShane HW, Patrick RT, Donald DE, Hetzel PS, Harshbarger HG, Wood EH. Intracardiac surgery with the aid of a mechanical pump oxygenator system (Gibbon type): report of eight cases. *Mayo Clinic Proc* 1955;30:201-51
3. Bartels C, Gerdes A, Babin-Ebell J, Beyersdorf F, Boeken U, Doenst T, Feindt P, Heiermann M, Schlensak C, Sievers HH. Working Group on Extracorporeal Circulation and Mechanical Ventricular Assist Devices of the German Society for Thoracic and Cardiovascular Surgery. Cardiopulmonary bypass: evidence or experience based? *J Thorac Cardiovasc Surg* 2002;124:20-7
4. Mora-Mangano CT, Chow JL, Kanevsky M. Cardiopulmonary bypass and the anesthesiologist. In: Kaplan JA, Reich DL, Lake CL, Konstadt SN, eds. *Kaplan's cardiac anesthesia*, 5th ed. Philadelphia: Elsevier/Saunders, 2006: 853-88
5. Stammers AH, Mejak BL. An update on perfusion safety: does the type of perfusion practice affect the rate of incidents related to cardiopulmonary bypass? *Perfusion* 2001;16:189-98
6. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959;39:183-238
7. McCall ML. Cerebral circulation and metabolism in toxemia of pregnancy. Observations on the effects of Veratum viride and apresoline (1-hydrazinophthalazine). *Am J Obstet Gynecol* 1953;66:1015-30
8. Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of PaCO<sub>2</sub>. *Anesth Analg* 1987;66:825-32
9. Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, Freeman AM. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1984;38:592-600
10. Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM. Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke* 1994;25: 1985-8
11. Waldermar G, Schmidt JF, Andersen AR, Vorsstrup S, Ibsen H, Paulson OB. Angiotensin converting enzyme inhibition and cerebral blood flow autoregulation in normotensive and hypertensive man. *J Hypertens* 1989;7:229-35

12. Olsen KS, Svenden LB, Larsen FS, Paulson OB. Effect of labetalol on cerebral blood flow, oxygen metabolism, and autoregulation in healthy humans. *Br J Anaesth* 1995;75:51-4
13. Standgaard S. Autoregulation of cerebral blood flow in hypertensive patients. *Circulation* 1976;53:720-7
14. Javid H, Tufo HM, Najafi H, Dye WS, Hunter JA, Julian OC. Neurologic abnormalities following open heart surgery. *J Thorac Cardiovasc* 1969;58:502-9
15. Tufo HM, Ostfeld AM, Shekelle R. Central nervous system dysfunction following open heart surgery. *JAMA* 1970;212:1333-40
16. Lee LW Jr, Brady MP, Rowe JM, Miller WC Jr. Effects of extracorporeal circulation upon behavior, personality, and brain function. II. Hemodynamic, metabolic, and psychometric correlations. *Ann Surg* 1971;173:1013-23
17. Ellis RJ, Wigniewski A, Potts R, Calhoun C, Loucks P, Wells MR. Reduction of flow rate and arterial pressure at moderate hypothermia does not result in cerebral dysfunction. *J Thorac Cardiovasc Surg* 1980;79:173-80
18. Sotaniemi KA, Juolasmas A, Hokkanen ET. Neuropsychologic outcome after open-heart surgery. *Arch Neurol* 1981;38:2-8
19. Fish KJ, Helms KN, Sernquist FH, van Steennis C, Linet OI, Hilberman M, Mitchell RS, Jamieson SW, Miller DC, Tinklenberg JS. A prospective, randomized study of the effects of prostacyclin on neuropsychologic dysfunction after coronary artery operation. *J Thorac Cardiovasc Surg* 1987;93:609-15
20. Slogoff S, Reul GJ, Keats AS, Curry GR, Crum ME, Elmquist BA, Giesecke NM, Jistel JR, Rogers LK, Soderberg JD, Edelman SK. Role of perfusion pressure and flow in major organ dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1990;50:911-8
21. Hill SE, van Wermeskerken GK, Lardenoye JW, Phillips-Bute B, Smith PK, Reves JG, Newman MF. Intraoperative physiologic variables and outcome in cardiac surgery. Part I. In-hospital mortality. *Ann Thorac Surg* 2000;69:1070-6
22. van Wermeskerken GK, Lardenoye JW, Hill SE, Grocott HP, Phillips-Bute B, Smith PK, Reves JG, Newman MF. Intraoperative physiologic variables and outcome in cardiac surgery. Part II. Neurologic outcome. *Ann Thorac Surg* 2000;69:1077-83
23. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. *Anesth Analg* 1999;89:814-22
24. Gardner TJ, Horneffer PJ, Manolio TA, Pearson TA, Gott VL, Baumgartner WA, Borkon AM, Watkins L Jr, Reitz BA. Stroke following coronary artery bypass grafting. A ten-year study. *Ann Thorac Surg* 1985;40:574-81
25. Fisher UM, Weissenberger WK, Warters RD, Geissler HJ, Allen SJ, Mehlhorn U. Impact of cardiopulmonary bypass management on postcardiac surgery renal function. *Perfusion* 2002;17:401-6
26. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, Hartman GS, Yao FS, Hollenberg JP, Barbut D. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *J Thorac Cardiovasc Surg* 1995;110:1302-11
27. Hartman GS, Yao FSF, Bruefach M, Barbut D, Peterson JC, Purcell MH, Charlson ME, Gold JP, Thomas SJ, Szatrowski TP. Severity of atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: a prospective study. *Anesth Analg* 1996;83:701-8
28. Goto T, Yoshitake A, Baba T, Shibata Y, Sakata R, Uozumi H. Cerebral ischemic disorders and cerebral oxygen balance during cardiopulmonary bypass surgery: preoperative evaluation using magnetic resonance imaging and angiography. *Anesth Analg* 1997;84:5-11
29. Newman MF, Kramer D, Croughwell ND, Sanderson I, Blumenthal JA, White WD, Smith LR, Towner EA, Reves JG. Differential age effects of mean arterial pressure and re-warming on cognitive dysfunction after cardiac surgery. *Anesth Analg* 1995;81:236-42
30. Schell RM, Kern FH, Greeley WJ, Schulman SR, Frasco PE, Croughwell ND, Newman M, Reves JG. Cerebral blood flow and metabolism during cardiopulmonary bypass. *Anesth Analg* 1993;76:849-65
31. Croughwell N, Lyth M, Quill TJ, Newman M, Greeley WJ, Smith LR, Reves JG. Diabetic patients have abnormal cerebral autoregulation during cardiopulmonary bypass. *Circulation* 1990;82:IV407-IV412
32. Cook DJ, Proper JA, Orszulak TA, Daly RC, Oliver WC. Effect of pump flow rate on cerebral blood flow during hypothermic cardiopulmonary bypass in adults. *J Cardiothorac Vasc Anesth* 1997;11:415-19
33. Rogers AT, Prough DS, Roy RC, Gravlee GP, Stump DA, Cordell AR, Phipps J, Taylor CL. Cerebrovascular and cerebral metabolic effects of alterations in perfusion flow rate during hypothermic cardiopulmonary bypass in man. *J Thorac Cardiovasc Surg* 1992;103:363-8
34. Soma Y, Hirofani T, Yozu R, Onoguchi K, Misumi T, Kawada K, Inoue T. A clinical study of cerebral circulation during extracorporeal circulation. *J Thorac Cardiovasc Surg* 1989;97:187-93
35. Schwartz AE, Sandhu AA, Kaplon RJ, Young WL, Jonassen AE, Adams DC, Edwards NM, Sistino JJ, Kwiatkowski P, Michler RE. Cerebral blood flow is determined by arterial pressure and not cardiopulmonary bypass flow rate. *Ann Thorac Surg* 1995;60:165-70
36. Sungurtekin H, Boston US, Cook DJ. Bypass flow, mean arterial pressure, and cerebral perfusion during cardiopulmonary bypass in dogs. *J Cardiothorac Vasc Anesth* 2000;14:25-28
37. Fox LS, Blackstone EH, Kirklin JW, Bishop SP, Bergdahl LA, Bradley EL. Relationship of brain blood flow and oxygen consumption to perfusion flow rate during profoundly hypothermic cardiopulmonary bypass. An experimental study. *J Thorac Cardiovasc Surg* 1984;87:658-64
38. Tanaka J, Shiki K, Asou T, Yasui H, Tokunaga K. Cerebral autoregulation during deep hypothermic nonpulsatile cardiopulmonary bypass with selective cerebral perfusion in dogs. *J Thorac Cardiovasc Surg* 1988;95:124-32
39. Bastien O, Piriou V, Aouifi A, Flamens C, Evans R, Lehot JJ. Relative importance of flow versus pressure in splanchnic perfusion during cardiopulmonary bypass in rabbits. *Anesthesiology* 2000;92:457-64
40. O'Dwyer C, Woodson LC, Conroy BP, Lin CY, Deyo DJ, Uchida T, Johnston WE. Regional perfusion abnormalities with phenylephrine during normothermic bypass. *Ann Thorac Surg* 1997;63:728-35
41. Mackay JH, Feerick AE, Woodson LC, Lin CY, Deyo DJ, Uchida T, Johnston WE. Increasing organ blood flow during cardiopulmonary bypass in pigs: comparison of dopamine and perfusion pressure. *Crit Care Med* 1995;23:1090-8
42. Kolkka R, Hilberman M. Neurologic dysfunction following cardiac operation with low-flow, low-pressure cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1980;79:432-7
43. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg* 2002;74:1180-6
44. Kuduvalli M, Oo AY, Newall N, Greyson AD, Jackson M, Desmond MJ, Fabri BM, Rashid A. Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2005;27:592-8
45. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, Blackstone EH. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. *Ann Thorac Surg* 2006;81:1650-7
46. Cohn LH, Fosberg AM, Anderson WP, Collins JJ. The effects of phlebotomy, hemodilution, and autologous transfusion on systemic oxygenation and whole blood utilization in open-heart surgery. *Chest* 1975;68:283-7
47. Lilleaasen P. Moderate and extreme haemodilution in open-heart surgery. *Scand J Cardiovasc Surg* 1977;11:97-103
48. Lowenstein E. Blood conservation in open heart surgery. *Cleve Clin Q* 1981;48:112-25
49. Cosgrove DM, Thurere RL, Lytle BW, Gill CG, Peter M, Loop FD. Determinants of blood utilization during myocardial revascularization. *Ann Thorac Surg* 1985;40:380-4
50. DeFoe GR, Ross CS, Olmstead EM, Surgenor SD, Fillingner MP, Groom RC, Forest RJ, Pieroni JW, Warren CS, Bogosian ME, Krumholz CF, Clark C, Clough RA, Weldner PW, Lahey SJ, Leavitt BJ, Marrin CA, Charlesworth DC, Marshall P, O'Connor GT. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. *Ann Thorac Surg* 2001;71:769-76

51. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? *J Thorac Cardiovasc Surg* 2003;125:1438–50
52. Karkouti K, Beattie WS, Wijeyesundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karaski J, David TE. Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J Thorac Cardiovasc Surg* 2005;129:391–400
53. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Engloran M, Durham SJ, Shah A. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcomes. *Crit Care Med* 2005;33:1749–56
54. Swaminathan M, Philips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. *Ann Thorac Surg* 2003;76:784–92
55. Fang CW, Helm RE, Krieger KH, Rosengart TK, DuBois WJ, Sason C, Lesser ML, Isom OW, Gold JP. Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. *Circulation* 1997;96(9 suppl):III194–III199
56. Ranucci M, Biagioli B, Scolletta S, Grillone G, Cazzaniga A, Cattabriga I, Isgro G, Giomarelli P. Lowest hematocrit on cardiopulmonary bypass impairs the outcome in coronary surgery. *Tex Heart Inst J* 2006;33:300–5
57. Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeyesundera D, Ivanov J, Karski J. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *Ann Thorac Surg* 2005;80:1381–7
58. Mathew JP, Mackensen GB, Phillips-Bute B, Stafford-Smith M, Podgoreanu MV, Grocott HP, Hill SE, Smith PK, Blumenthal JA, Reves JG, Newman MF. Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. *Anesthesiology* 2007;107:577–84
59. Fransen E, Maessen J, Dentemer M, Senden N, Buurman W. Impact of blood transfusion on inflammatory mediator release in patients undergoing cardiac surgery. *Chest* 1999;116:1233–9
60. Leal-Noval SR, Jara-Lopez I, Garcia-Garmendia JL, Marin-Niebla A, Herruzo-Aviles A, Camacho-Larana P, Loscertales J. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgical patients. *Anesthesiology* 2003;98:815–22
61. Murphy PJ, Connery C, Hicks GL, Blumberg N. Homologous blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. *J Thorac Cardiovasc Surg* 1992;104:1092–9
62. Ottino G, Paulis R, Pansini S. Major sternal wound infection after open-heart surgery: a multi-varient analysis of risk factors in 2579 consecutive operative procedures. *Ann Thorac Surg* 1987;44:173–9
63. Blumberg N, Heal J. Transfusion and recipient immune function. *Arch Pathol Lab Med* 1989;113:246–53
64. Plochl W, Orszulak TA, Cook DJ, Sarpal RS, Dickerman DL. Support of mean arterial pressure during tepid cardiopulmonary bypass: effects of phenylephrine and pump flow on systemic oxygen supply and demand. *J Cardiothorac Vasc Anesth* 1999;13:441–5
65. Shibutani K, Komatsu T, Kubal K, Sanchala V, Kumar V, Bizzarri DV. Critical level of oxygen delivery in anesthetized man. *Crit Care Med* 1983;11:640–3
66. Dantzker DR, Foresman B, Gutierrez G. Oxygen supply and utilization relationships. A reevaluation. *Am Rev Respir Dis* 1991;143:675–9
67. Cavaliere F, Gennari A, Martinelli L, Zamparelli R, Schiavello R. The relationship between systemic oxygen uptake and delivery during moderate hypothermic cardiopulmonary bypass: critical values and effects of vasodilation by hydralazine. *Perfusion* 1995;10:315–21
68. Komatsu T, Shibutani K, Okamoto K, Kumar V, Kubal K, Sanchala V, Lees DE. Critical levels of oxygen delivery after cardiopulmonary bypass. *Crit Care Med* 1987;15:194–7
69. Parolari A, Alamanni F, Gherli T, Bertera A, Dainese L, Costa C, Schena M, Sisillo E, Spirito R, Porqueddu M, Rona P, Biglioli. Cardiopulmonary bypass and oxygen consumption: oxygen delivery and hemodynamics. *Ann Thorac Surg* 1999;67:1320–7
70. Alston R. Systemic oxygen uptake during hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1989;98:757–68
71. Fox LS, Blackstone EH, Kirklin JW, Stewart RW, Samuelson PN. Relationship of whole body oxygen consumption to perfusion flow rate during hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1982;83:239–48
72. Baraka AS, Baroody MA, Haroun ST, Sibai AA, Nawfal MF, Dabbous AS, Taha SK, el-Khatib RA. Effect of alpha-stat versus pH-stat strategy on oxyhemoglobin dissociation and whole-body oxygen consumption during hypothermic cardiopulmonary bypass. *Anesth Analg* 1992;74:32–7
73. Hickey RF, Hoar PF. Whole-body oxygen consumption during low-flow hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1983;86:903–6
74. Suttner S, Piper SN, Kumle B, Lang K, Röhm KD, Isgro F, Boldt J. Influence of allogeneic red blood cell transfusion compared with 100% oxygen ventilation on systemic oxygen transport and skeletal muscle oxygen tension after cardiac surgery. *Anesth Analg* 2004;99:2–11
75. Joachimsson PO, Sjöberg F, Forsman M, Johansson M, Ahn HC, Rutberg H. Adverse effects of hyperoxia during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1996;112:812–9
76. von Heymann C, Sander M, Foer A, Heinemann A, Spiess B, Braun J, Kramer M, Grosse J, Dohmen P, Dushe S, Halle J, Konertz WF, Wernecke KD, Spies C. The impact of a hematocrit of 20% during normothermic cardiopulmonary bypass for elective low risk coronary artery bypass graft surgery on oxygen delivery and clinical outcomes—a randomized controlled study. *Crit Care* 2006;10:R58
77. Liam BL, Plochl W, Cook DJ, Orszulak TA, Daly RC. Hemodilution and whole body oxygen balance during normothermic cardiopulmonary bypass in dogs. *J Thorac Cardiovasc Surg* 1998;115:1203–8
78. Boston US, Slater JM, Orszulak TA, Cook DJ. Hierarchy of regional oxygen delivery during cardiopulmonary bypass. *Ann Thorac Surg* 2001;71:260–4
79. Tao W, Zwischenberger JB, Nguyen TT, Vertrees RA, McDaniel LB, Nutt LK, Herndon DN, Kramer GC. Gut mucosal ischemia during normothermic cardiopulmonary bypass results from blood flow redistribution and increased oxygen demand. *J Thorac Cardiovasc Surg* 1995;110:819–28
80. Gardeback M, Settergren G, Brodin LA, Jorfeldt L, Galuska D, Ekberg K, Wahren J. Splanchnic blood flow and oxygen uptake during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2002;16:308–15
81. Haisjackl M, Birnbaum J, Redlin M, Schmutzler M, Waldenberger F, Lochs H, Konertz W, Kox W. Splanchnic oxygen transport and lactate metabolism during normothermic cardiopulmonary bypass in humans. *Anesth Analg* 1998;86:22–7
82. Sicsic JC, Duranteau J, Corbineau H, Antoun S, Menestret P, Sitbon P, Leguerrier A, Logeais Y, Ecoffey C. Gastric mucosal oxygen delivery decreases during cardiopulmonary bypass despite constant systemic oxygen delivery. *Anesth Analg* 1998;86:455–60
83. Ranucci M, Romitti F, Isgro G, Cotza M, Brozzi S, Boncilli A, Ditta A. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. *Ann Thorac Surg* 2005;80:2213–20
84. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia: its possible role in cardiac surgery—an investigation of factors governing survival in dogs at low body temperatures. *Ann Surg* 1950;132:849–66
85. Bigelow WG, Lindsay WK, Harrison RC. Oxygen transport and utilization in dogs at low body temperatures. *Am J Physiol* 1950;160:125–37
86. The Warm Heart Investigators. Randomized trial of normothermic versus hypothermic coronary bypass surgery. *Lancet* 1994;343:559–63
87. Martin TD, Craver JM, Gott JP, Weintraub WS, Ramsay J, Mora CT, Guyton RA. Prospective, randomized trial of retrograde warm blood cardioplegia: myocardial benefit and neurological threat. *Ann Thorac Surg* 1994;57:298–304
88. Rees K, Beranek-Stanley M, Burke M, Ebrahim S. Hypothermia to reduce neurologic damage following coronary artery bypass surgery. *Cochrane Database Syst Rev* 2006; CD002138



89. Christenson JT, Maurice J, Simonet F, Velebit V, Schmuziger M. Normothermic versus hypothermic perfusion during primary coronary artery bypass grafting. *Cardiovasc Surg* 1995;3:519-24
90. Lichtenstein SV, Ashe KA, el Dalati H, Cusimano RJ, Panos A, Slutsky AS. Warm heart surgery. *J Thorac Cardiovasc Surg* 1991;101:269-74
91. Nathan HJ, Parlea L, Dupuis JY, Hendry P, Williams KA, Rubens FD, Wells GA. Safety of deliberate intraoperative and postoperative hypothermia for patients undergoing coronary artery surgery: a randomized trial. *J Thorac Cardiovasc Surg* 2004;127:1270-5
92. Birdi I, Regragui I, Izzat MB, Bryan AJ, Angelini GD. Influence of normothermic systemic perfusion during coronary artery bypass operations: a randomized prospective study. *J Thorac Cardiovasc Surg* 1997;114:475-81
93. Christakis GT, Koch JP, Deemar KA, Femes SE, Sinclair SE, Chen E, Salerno TA, Goldman BS, Lichtenstein SV. A randomized study of the systemic effects of warm heart surgery. *Ann Thorac Surg* 1992;54:449-59
94. Gozal Y, Glantz L, Luria MH, Milgater E, Simón D, Drenger B. Normothermic continuous blood cardioplegia improves electrophysiologic recovery after open heart surgery. *Anesthesiology* 1996;84:1298-306
95. Lehot JJ, Villard J, Piriz H, Philbin DM, Carry PY, Gauquelin G, Claustrat B, Sassolas G, Galliot J, Estanove S. Hemodynamic and hormonal responses to hypothermic and normothermic cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1992;6:132-9
96. Cook DJ, Oliver WC Jr, Orszulak TA, Daly RC. Vasoactive infusion requirements during normothermic and hypothermic cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1994;8:34
97. Regragui IA, Izzat MB, Birdi I, Lapsley M, Bryan AJ, Angelini GD. Cardiopulmonary bypass perfusion temperature does not influence perioperative renal function. *Ann Thorac Surg* 1995;60:160-4
98. Swaminathan M, East C, Phillips-Bute B, Newman MF, Reves JG, Smith PK, Stafford-Smith M. Report of a substudy on warm versus cold cardiopulmonary bypass: changes in creatinine clearance. *Ann Thorac Surg* 2001;72:1603-9
99. Boldt J, Knothe C, Zickmann B, Bill S, Dapper F, Hempelmann G. Platelet function in cardiac surgery: influence of temperature and aprotinin. *Ann Thorac Surg* 1993;55:652-8
100. Boldt J, Knothe C, Welters I, Dapper FL, Hempelmann G. Normothermic versus hypothermic bypass: do changes in coagulation differ? *Ann Thorac Surg* 1996;62:130-5
101. Engelman RM, Pleet AB, Rousou JA, Flack JE III, Deaton DW, Pekow PS, Gregory CA. Influence of cardiopulmonary bypass perfusion temperature on neurologic and hematologic function after coronary artery bypass grafting. *Ann Thorac Surg* 1999;67:1547-55
102. Stensrud PE, Nuttall GA, de Castro MA, Abel MD, Ereth MH, Oliver WC Jr, Bryant SC, Schaff HV. A prospective, randomized study of cardiopulmonary bypass temperature and blood transfusion. *Ann Thorac Surg* 1999;67:711-5
103. Tonz M, Mihaljevic T, von Segesser LK, Schmid ER, Joller-Jemelka HI, Pei P, Turina MI. Normothermia versus hypothermia during cardiopulmonary bypass: a randomized, controlled trial. *Ann Thorac Surg* 1995;59:137-43
104. Cook DJ. Changing temperature management for cardiopulmonary bypass. *Anesth Analg* 1999;88:1254-71
105. Nathan HJ, Wells GA, Munson JL, Wozney D. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass. A randomized trial. *Circulation* 2001;104: (12 suppl 1):I85-I91
106. Grigore AM, Grocott HP, Mathew JP, Phillips-Bute B, Stanley TO, Butler A, Landolfo KP, Reves JG, Blumenthal JA, Newman MF. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. *Anesth Analg* 2002;94:4-10
107. Nathan HJ, Rodriguez R, Wozny D, Dupuis JY, Rubens FD, Bryson GL, Wells G. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. *J Thorac Cardiovasc Surg* 2007;133:1206-11
108. Ji B, Undar A. An evaluation of the benefits of pulsatile versus nonpulsatile perfusion during cardiopulmonary bypass procedures in pediatric and adult cardiac patients. *ASAIO J* 2006;52:357-61
109. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. I. Mortality and cardiovascular morbidity. *J Thorac Cardiovasc Surg* 1995;110:340-8
110. Taylor KM, Bain WH, Davidson KG, Turner MA. Comparative clinical study and pulsatile and non-pulsatile perfusion in 350 consecutive patients. *Thorax* 1982;37:324-30
111. Abramov D, Tamariz M, Serrick CI, Sharp E, Noel D, Harwood S, Christakis GT, Goldman BS. The influence of cardiopulmonary bypass flow characteristics on the clinical outcome of 1820 coronary bypass patients. *Can J Cardiol* 2003;19:237-43
112. Song Z, Wang C, Stammers AH. Clinical comparison of pulsatile and nonpulsatile perfusion during cardiopulmonary bypass. *J Extra Corpor Technol* 1997;29:170-5
113. Takahara Y, Sudo Y, Nakano H, Sato T, Ishikawa H, Nakajima N. Strategy for reduction of stroke incidence in coronary bypass patients with cerebral lesions. Early results and mid-term morbidity using pulsatile perfusion. *Jpn J Thorac Cardiovasc Surg* 2000;48:551-6
114. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. *J Thorac Cardiovasc Surg* 1995;110:349-62
115. Henze T, Stephan H, Sonntag H. Cerebral dysfunction following extracorporeal circulation for aortocoronary bypass surgery: no differences in neuropsychological outcome after pulsatile versus nonpulsatile flow. *Thorac Cardiovasc Surg* 1990;38:65-8
116. Kocakulak M, Akin G, Kucukaksu S, Tarcan O, Pikin E. Pulsatile flow improves renal function in high-risk cardiac operations. *Blood Purif* 2005;23:263-7
117. Badner NH, Murkin JM, Lok P. Differences in pH management and pulsatile/nonpulsatile perfusion during cardiopulmonary bypass do not influence renal function. *Anesth Analg* 1992;75:696-701
118. Hamulu A, Atay Y, Yadi T, Diczil B, Bakalim T, Buket S, Bilkay O. Effects of flow types in cardiopulmonary bypass on gastric intramucosal pH. *Perfusion* 1998;13:129-35
119. Gaer JA, Shaw AD, Wild R, Swift RI, Munsch CM, Smith PL, Taylor KM. Effect of cardiopulmonary bypass on gastrointestinal perfusion and function. *Ann Thorac Surg* 1994;57:371-5
120. Mathie RT, Ohri SK, Batten JJ, Peters AM, Keogh BE. Hepatic blood flow during cardiopulmonary bypass operations: the effect of temperature and pulsatility. *J Thorac Cardiovasc Surg* 1997;114:292-3
121. Sezai A, Shiono M, Nakata K, Hata M, Iida M, Saito A, Hattori T, Wakui S, Soeda M, Taoka M, Umeda T, Negishi N, Sezai Y. Effects of pulsatile CPB on interleukin-8 and endothelin-1 levels. *Artif Organs* 2005;29:708-13
122. Driessen JJ, Dhaese H, Fransen G, Verrelst P, Rondelst P, Gevaert L, van Becelaere M, Schelstraete E. Pulsatile compared to nonpulsatile perfusion using a centrifugal pump for cardiopulmonary bypass during coronary artery bypass grafting. Effects on systemic haemodynamics, oxygenation, and inflammatory response parameters. *Perfusion* 1995;10:3-12
123. Dapper F, Neppel H, Wozniak G, Strube I, Zickmann B, Hehrlein FW, Neuhof H. Effects of pulsatile and nonpulsatile perfusion mode during extracorporeal circulation: a comparative clinical study. *Thorac Cardiovasc Surg* 1992;40:345-51
124. Zamparelli R, De Paulis S, Martinelli L, Rossi M, Scapigliati A, Sciarra M, Meo F, Schiavello R. Pulsatile normothermic cardiopulmonary bypass and plasma catecholamine levels. *Perfusion* 2000;15:217-23
125. Canivet JL, Larbuisson R, Damas P, Blaffart F, Faymonville M, Limet R, Lamy M. Plasma rennin activity and urine beta 2-microglobulin during and after cardiopulmonary bypass: pulsatile vs non-pulsatile perfusion. *Eur Heart J* 1990;11:1079-82
126. Goto M, Kudoh K, Minami S, Nukariya M, Sasaguri S, Watanabe M, Hosoda Y. The renin-aldosterone system and hematologic changes during pulsatile and nonpulsatile cardiopulmonary bypass. *Artif Organs* 1993;17:318-22
127. Alghamdi AA, Latter DA. Pulsatile versus nonpulsatile cardiopulmonary bypass flow: an evidence-based approach. *J Card Surg* 2006;21:347-54
128. Mavroudis C. To pulse or not to pulse. *Ann Thorac Surg* 1978;25:259-62

129. Undar A, Rosenberg G, Myers JL. Major factors in the controversy of pulsatile versus nonpulsatile flow during acute and chronic support. *ASAIO J* 2005;51:173-5
130. Undar A, Masai T, Frazier OH, Fraser CD. Pulsatile and nonpulsatile flows can be quantified in terms of energy equivalent pressure during cardiopulmonary bypass for direct comparisons. *ASAIO J* 1999;45:610-4
131. Undar A. Pulsatile versus nonpulsatile cardiopulmonary bypass procedures in neonates and infants: from bench to clinical practice. *ASAIO J* 2005;51:6-10
132. Gourlay T, Taylor KM. Pulsatile flow and membrane oxygenators. *Perfusion* 1994;9:189-96
133. Undar A, Lodge AJ, Daggett CW, Runge TM, Ungerleider RM, Cahoon JH. The type of aortic cannula and membrane oxygenator affect the pulsatile waveform morphology produced by a neonate-infant cardiopulmonary bypass system *in vivo*. *Artif Organs* 1998;22:681-6
134. Hogue CW Jr, Palin CA, Arrowsmith JE. Cardiopulmonary bypass management and neurologic outcomes: an evidence-based appraisal of current practices. *Anesth Analg* 2006;103:21-37
135. Tayama E, Raskins SA, Nose Y. Blood Pumps. In: Gravlee GP, Davis RF, Kurusz M, Utley JR, eds. *Cardiopulmonary bypass principles and practice*. 2nd ed. Philadelphia: Liipncott, Williams & Wilkins, 2000:37-68
136. Kurusz M. Roller pump induced tubing wear: another argument in favor of arterial line filtration. *J Extra Corpor Technol* 1980;12:49-59
137. Peek GJ, Thompson A, Killer HM, Firmin RK. Spallation performance of extracorporeal membrane oxygenation tubing. *Perfusion* 2000;15:457-66
138. Morin BJ, Riley JB. Thrombus formation in centrifugal pumps. *J Extra Corpor Technol* 1992;24:20-5
139. Oku T, Haraski H, Smith W, Nose Y. Hemolysis. A comparative study of four nonpulsatile pumps. *ASAIO Trans* 1988;34:500-4
140. Jakob H, Kutschera Y, Palzer B, Prellwitz W, Oelert H. In-vitro assessment of centrifugal pumps for ventricular assist. *Artif Organs* 1990;14:278-83
141. Englehardt H, Vogelsang B, Reul H, Rau G. Hydrodynamical and hemodynamical evaluation of rotary blood pumps. Proceedings of the International Workshop on Rotary Blood Pumps. Thoma H, Schima H, eds. Vienna, 1988
142. Hoerr HR, Kraemer MF, Williams JL, Sherman ML, Riley JB, Crowley JC, Soronen SW. *In vitro* comparison of the blood handling by the constrained vortex and twin roller pumps. *J Extra Corpor Technol* 1987;19:316-21
143. Kress DC, Cohen DJ, Swanson DK, Hegge JO, Young JW, Watson KM, Rasmussen PW, Berkoff HA. Pump-induced hemolysis in rabbit model of neonatal ECMO. *Trans Am Soc Artif Intern Organs* 1987;33:446-52
144. Tamari Y, Lee-Sensiba K, Leonard EF, Parnell I, Vortolani AJ. The effects of pressure and flow on hemolysis caused by bio-medical centrifugal pumps and roller pumps. *J Thorac Cardiovasc Surg* 1993;106:997-1007
145. Rawn D, Harris H, Riley J, Yoda D, Blackwell M. An under-occluded roller pump is less hemolytic than a centrifugal pump. *J Extra Corpor Technol* 1997;29:15-18
146. Horton AM, Butt W. Pump-induced haemolysis: is the constrained vortex pump better or worse than the roller pump? *Perfusion* 1992;7:103-8
147. Moen O, Fosse E, Braten J, Anderson C, Fagersol MK, Venge P, Hegases K, Mollnes TE. Roller and centrifugal pumps compared *in vitro* with regard to hemolysis, granulocyte, and complement activation. *Perfusion* 1994;9:109-17
148. Palder SB, Shaheen KW, Whittlesey GS, Nowlen TT, Kundu SK, Klein MD. Prolonged extracorporeal membrane oxygenation in sheep with hollow-fiber oxygenators and centrifugal pumps. *Trans Am Soc Artif Intern Org* 1988;34:820-2
149. Wheeldon DR, Bethune DW, Gill RD. Vortex pumping for routine cardiac surgery: a comparative study. *Perfusion* 1990;5:135-43
150. Parault BG, Conrad SA. The effect of extracorporeal circulation time and patient age on platelet retention during cardiopulmonary bypass: a comparison of roller and centrifugal pumps. *J Extra Corpor Technol* 1991;23:34-38
151. Salo M, Perttala J, Pulkki K, Gronroos J, Mertsola J, Peltola O, Nevalainen T. Proinflammatory mediator response to coronary bypass surgery using a centrifugal or a roller pump. *J Extra Corpor Technol* 1995;27:146-51
152. Klein M, Dauben HP, Schulte HD, Gams E. Centrifugal pumping during routine open heart surgery improves clinical outcome. *Artif Organs* 1998;22:326-36
153. Ashraf S, Bhattacharya K, Zacharias S, Kaul P, Kay PH, Watterson KG. Serum S100beta release after coronary artery bypass grafting: roller versus centrifugal pump. *Ann Thorac Surg* 1998;66:1958-62
154. Dickinson TA, Prichard J, Rieckens F. A comparison of the benefits of roller pump versus constrained vortex pump in adult open-heart operations utilizing outcomes research. *J Extra Corpor Technol* 1994;26:108-13
155. Scott DA, Silbert BS, Doyle TJ, Blyth C, Borton MC, O'Brien JL, de L Horne DJ. Centrifugal versus roller head pumps for cardiopulmonary bypass: effect on early neuropsychologic outcomes after coronary artery surgery. *J Cardiothorac Vasc Anesth* 2002;16:715-22
156. DeBois W, Brennan R, Wein E, Isom OW, Gold JP. Centrifugal pumping: the patient outcome benefits following coronary artery bypass surgery. *J Extra Corpor Technol* 1995;27:77-80
157. Alamanni F, Parolari A, Zanobini M, Porqueddu M, Dainese L, Bertera A, Costa C, Fusari M, Spirito R, Biglioli P. Centrifugal pump and reduction of neurological risk in adult cardiac surgery. *J Extra Corpor Technol* 2001;33:4-9
158. Babin-Ebell J, Misoph M, Müllges W, Neukam K, Elert O. Reduced release of tissue factor by application of a centrifugal pump during cardiopulmonary bypass. *Heart Vessels* 1998;13:147-51
159. Baufreton C, Intrator L, Jansen PG, te Velthuis H, Le Besnerais P, Vonk A, Farcet JP, Wildevuur CR, Loisanse DY. Inflammatory response to cardiopulmonary bypass using roller or centrifugal pumps. *Ann Thorac Surg* 1999;67:972-7
160. Lindholm L, Westerberg M, Bengtsson A, Ekroth R, Jensen E, Jeppsson A. A closed perfusion system with heparin coating and centrifugal pump improves cardiopulmonary bypass biocompatibility in elderly patients. *Ann Thorac Surg* 2004;78:2131-8
161. Moen O, Fosse E, Dregelid E, Brockmeier V, Andersson C, Hogasen K, Venge P, Mollnes TE, Kierulf P. Centrifugal pump and heparin coating improves cardiopulmonary bypass biocompatibility. *Ann Thorac Surg* 1996;62:1134-40
162. Driessen JJ, Fransen G, Rondelez L, Schelstraete E, Gevaert L. Comparison of the standard roller pump and a pulsatile centrifugal pump for extracorporeal circulation during routine coronary artery bypass grafting. *Perfusion* 1991;6:303-11
163. Wahba A, Phillip A, Bauer MF, Aebert H, Birnbaum DE. The blood saving potential of vortex versus roller pump with and without aprotinin. *Perfusion* 1995;10:111-41
164. Macey MG, McCarthy DA, Trivedi UH, Venn GE, Chambers DJ, Brown KA. Neutrophil adhesion molecule expression during cardiopulmonary bypass: a comparative study of roller and centrifugal pumps. *Perfusion* 1997;12:293-301
165. Ashraf SS, Tian Y, Cowan D, Shaikh R, Parsloe M, Martin P, Watterson KG. Proinflammatory cytokine release during pediatric cardiopulmonary bypass: influence of centrifugal and roller pumps. *J Cardiothorac Vasc Anesth* 1997;11:718-22
166. Ashraf SS, Butler J, Tian Y, Cowan D, Lintin S, Saunders NR, Watterson KG, Martin PG. Inflammatory mediators in adults undergoing cardiopulmonary bypass: comparison of centrifugal and roller pumps. *Ann Thorac Surg* 1998;65:480-4
167. Andersen LS, Nygreen O, Grong L, Leirvaag B, Holmsen H. Comparison of the centrifugal and roller pump in elective coronary artery bypass surgery—a prospective randomized study with special emphasis upon platelet activation. *Scand Cardiovasc J* 2003;37:356-62
168. Morgan IS, Codispoti M, Sanger K, Mankad PS. Superiority of centrifugal pump over roller pump in paediatric cardiac surgery: prospective randomized trial. *Eur J Cardiothorac Surg* 1998;13:526-32
169. Jensen E, Andreasson S, Bengtsson A, Berggren H, Ekroth R, Lindholm L, Ouchterlony J. Influence of two different perfusion systems on inflammatory response in pediatric heart surgery. *Ann Thorac Surg* 2003;75:919-25
170. Lilly KJ, O'Gara PJ, Treanor PR, Reardon D, Crowley R, Hunter C, Shapira OM, Aldea GS, Lazar HL, Shemin RJ. Cardiopulmonary bypass: it's not the size, it's how you use it! review of a comprehensive blood-conservation strategy. *J Extra Corpor Technol* 2004;36:263-8

171. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA, Haan CK, Royston BD, Bridges CR, Higgins RS, Despotis G, Brown JR; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, Body S. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg* 2007;83(5 Suppl):S27-S86
172. Mejak B, Stammers A, Rauch E, Vang S, Viessman T. A retrospective study on perfusion incidents and safety devices. *Perfusion* 2000;15:51-61
173. Gott VL, Whiffen JD, Koepke DE, Daggett RL, Boake WC, Young WP. Techniques of applying a graphite-benzalkonium-heparin coating to various plastics and metals. *Trans Am Soc Artif Intern Organs* 1964;10:213-7
174. Aldea GS, Doursounian M, O'Gara P, Treanor P, Shapira OM, Lazar HL, Shemin RJ. Heparin-bonded circuits with a reduced anticoagulation protocol in primary CABG: a prospective, randomized study. *Ann Thorac Surg* 1996;62:410-18
175. von Segesser LK, Weiss BM, Garcia E, von Felten A, Turina MI. Reduction and elimination of systemic heparinization during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1992;103:790-9
176. Sinci V, Kalaycioglu S, Gunaydin S, Imren Y, Gokgoz L, Soncul H, Ersoz A. Evaluation of heparin-coated circuits with full heparin dose strategy. *Ann Thorac Cardiovasc Surg* 1999;5:156-63
177. von Segesser LK, Weiss BM, Pasic M, Garcia E, Turina MI. Risk and benefit of low systemic heparinization during open heart operations. *Ann Thorac Surg* 1994;58:391-8
178. Kuitunen AH, Heikkila LJ, Salmenpera MT. Cardiopulmonary bypass with heparin-coated circuits and reduced systemic anticoagulation. *Ann Thorac Surg* 1997;63:438-44
179. Stammers AH, Christensen KA, Lynch J, Zavdil DP, Deptula JJ, Sydzyk RT. Quantitative evaluation of heparin-coated versus non-heparin-coated bypass circuits during cardiopulmonary bypass. *J Extra Corpor Technol* 1999;31:135-41
180. Grossi EA, Kallenbach K, Chau S, Derivaux CC, Aguinaga MG, Steinberg BM, Kim D, Iyer S, Tayyarah M, Artman M, Gallo-way AC, Colvin SB. Impact of heparin bonding on pediatric cardiopulmonary bypass: a prospective randomized study. *Ann Thorac Surg* 2000;70:191-6
181. Ozawa T, Yoshihara K, Koyama N, Yamazaki S, Takanashi Y. Superior biocompatibility of heparin-bonded circuits in pediatric cardiopulmonary bypass. *Jpn J Thorac Cardiovasc Surg* 1999;47:592-9
182. Jensen E, Andreasson S, Bengtsson A, Berggren H, Ekroth R, Larsson LE, Ouchterlony J. Changes in hemostasis during pediatric heart surgery: impact of a biocompatible heparin-coated perfusion system. *Ann Thorac Surg* 2004;77:962-7
183. Boonstra PW, Gu YJ, Akkerman C, Haan J, Huyzen R, van Oeveren W. Heparin coating of an extracorporeal circuit partly improves hemostasis after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1994;107:289-92
184. Thelin S, Bagge L, Hultman J, Borowiec J, Nilsson L, Thorelius J. Heparin-coated cardiopulmonary bypass circuits reduce blood cell trauma. Experiments in the pig. *Eur J Cardiothorac Surg* 1991;5:486-91
185. van der Kamp KW, van Oeveren W. Contact, coagulation and platelet interaction with heparin treated equipment during heart surgery. *Int J Artif Organs* 1993;16:836-42
186. Palatianos GM, Dewanjee MK, Smith W, Novak S, Hsu LC, Kapadvanjwala M, Sfakianakis GN, Kaiser GA. Platelet preservation during cardiopulmonary bypass with iloprost and Duraflo-II heparin-coated surfaces. *ASAIO Trans* 1991;37:620-2
187. Svennevig JL, Geiran OR, Karlsen H, Pederson T, Mollnes TE, Kongsgard U, Froyssaker T. Complement activation during extracorporeal circulation. *In vitro* comparison of Duraflo II heparin-coated and uncoated oxygenator circuits. *J Thorac Cardiovasc Surg* 1993;106:466-72
188. Fosse E, Thelin S, Svennevig JL, Jansen P, Mollnes TE, Hack E, Venge P, Moen O, Brockmeier V, Dregelid E, Halden E, Hagman L, Videm V, Pedersen T, Moer B. Duraflo II coating of cardiopulmonary bypass circuits reduces complement activation, but does not affect the release of granulocyte enzymes: a European multicentre study. *Eur J Cardiothorac Surg* 1997;11:320-7
189. Videm V, Svennevig JL, Fosse E, Semb G, Osterud A, Mollnes TE. Reduced complement activation with heparin-coated oxygenator and tubings in coronary bypass operations. *J Thorac Cardiovasc Surg* 1992;103:806-13
190. Mollnes TE, Videm V, Gotze O, Harboe M, Oppermann M. Formation of C5a during cardiopulmonary bypass: inhibition by precoating with heparin. *Ann Thorac Surg* 1991;52:92-7
191. Gu YJ, van Oeveren W, Akkerman C, Boonstra PW, Huyzen RJ, Wildevuur CR. Heparin-coated circuits reduce the inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg* 1993;55:917-22
192. Belboul A, Akbar O, Lofgren C, Jungbeck M, Storm C, Roberts A. Improved blood cellular biocompatibility with heparin coated circuits during cardiopulmonary bypass. *J Cardiovasc Surg* 2000;41:357-62
193. Moen O, Fosse E, Brockmeier V, Andersson C, Mollnes TE, Hogasen K, Venge P. Disparity in blood activation by two different heparin-coated cardiopulmonary bypass systems. *Ann Thorac Surg* 1995;60:1317-23
194. Moen O, Hogasen K, Fosse E, Dregelid E, Brockmeier V, Venge P, Harboe M, Mollnes TE. Attenuation of changes in leukocyte surface markers and complement activation with heparin-coated cardiopulmonary bypass. *Ann Thorac Surg* 1997;63:105-11
195. Ranucci M, Mazzucco A, Pessotto R, Grillone G, Casati V, Porreca L, Maugeri R, Meli M, Magagna P, Cirri S, Giomarelli P, Lorusso R, de Jong A. Heparin-coated circuits for high-risk patients: a multicenter, prospective, randomized trial. *Ann Thorac Surg* 1999;67:994-1000
196. Mahoney CB. Heparin-bonded circuits: clinical outcomes and costs. *Perfusion* 1998;13:192-204
197. Mahoney CB, Lemole GM. Transfusion after coronary artery bypass surgery: the impact of heparin-bonded circuits. *Eur J Cardiothorac Surg* 1999;16:206-10
198. Ranucci M, Cirri S, Conti D, Ditta A, Boncilli A, Frigiola A, Menicanti L. Beneficial effects of Duraflo II heparin-coated circuits on postperfusion lung dysfunction. *Ann Thorac Surg* 1996;61:76-81
199. Redmond JM, Gillinov AM, Stuart RS, Zehr KJ, Winkelstein JA, Herskowitz A, Cameron DE, Baumgartner WA. Heparin-coated bypass circuits reduce pulmonary injury. *Ann Thorac Surg* 1993;56:474-8
200. Heyer EJ, Lee KS, Manspeizer HE, Mongero L, Spanier TB, Caliste X, Esrig B, Smith C. Heparin-bonded cardiopulmonary bypass circuits reduce cognitive dysfunction. *J Cardiothorac Vasc Anesth* 2002;16:37-42
201. Svenmarker S, Haggmark S, Jansson E, Lindholm R, Appelblad M, Sandström E, Aberg T. Use of heparin-bonded circuits in cardiopulmonary bypass improves clinical outcome. *Scand Cardiovasc J* 2002;36:241-6
202. Mongero LB, Beck JR, Manspeizer HE, Heyer EJ, Lee K, Spanier TA, Smith CR. Cardiac surgical patients exposed to heparin-bonded circuits develop less postoperative cerebral dysfunction than patients exposed to non-heparin-bonded circuits. *Perfusion* 2001;16:107-11
203. Muehrcke DD, McCarthy PM, Kottke-Marchant K, Harasaki H, Pierre-Yared J, Borsh JA, Ogella DA, Cosgrove DM. Biocompatibility of heparin-coated extracorporeal bypass circuits: a randomized, masked clinical trial. *J Thorac Cardiovasc Surg* 1996;112:472-83
204. McCarthy PM, Yared JP, Foster RC, Ogella DA, Borsh JA, Cosgrove DM III. A prospective randomized trial of Duraflo II heparin-coated circuits in cardiac reoperations. *Ann Thorac Surg* 1999;67:1268-73
205. Mangoush O, Purkayastha S, Haj-Yahia S, Kinross J, Hayward M, Bartolozzi F, Darzi A, Athanasiou T. Heparin-bonded circuits versus nonheparin-bonded circuits: an evaluation of their effect on clinical outcomes. *Eur J Cardiothorac Surg* 2007;31:1058-69
206. Shann KG, Likosky DS, Murkin JM, Baker RA, Baribeau YR, DeFoe GR, Dickinson TA, Gardner TJ, Grocott HP, O'Connor GT, Rosinski DJ, Sellke FW, Willcox TW. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. *J Thorac Cardiovasc Surg* 2006;132:283-90
207. Haworth WS. The development of the modern oxygenator. *Ann Thorac Surg* 2003;76:S2216-S2219



208. Taylor RL, Borger MA, Weisel RD, Fedorko L, Feindel CM. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. *Ann Thorac Surg* 1999;68:89–93
209. Rider SP, Simon LV, Rice BJ, Poulton CC. Assisted venous drainage, venous air, and gaseous microemboli transmission into the arterial line: an in-vitro study. *J Extra Corpor Technol* 1998;30:160–5
210. Willcox TW, Mitchell SJ, Gorman DF. Venous air in the bypass circuit: a source of arterial line emboli exacerbated by vacuum-assisted drainage. *Ann Thorac Surg* 1999;68:1285–9
211. Jones TJ, Deal DD, Vernon JC, Blackburn N, Stump DA. Does vacuum-assisted venous drainage increase gaseous microemboli during cardiopulmonary bypass? *Ann Thorac Surg* 2002;74:2132–7
212. Weitkemper HH, Oppermann B, Spilker A, Knobl HJ, Körfer R. Gaseous microemboli and the influence of microporous membrane oxygenators. *J Extra Corpor Technol* 2005;37:256–64
213. Dickinson T, Riley JB, Crowley JC, Zabetakis PM. In vitro evaluation of the air separation ability of four cardiovascular manufacturer extracorporeal circuit designs. *J Extra Corpor Technol* 2006;38:206–13
214. Horton S, Thuys C, Bennett M, Augustin S, Rosenberg M, Brizard C. Experience with the Jostra Rotaflow and QuadroxD oxygenator for ECMO. *Perfusion* 2004;19:17–23
215. Schönberger JP, Everts PA, Hoffmann JJ. Systemic blood activation with open and closed venous reservoirs. *Ann Thorac Surg* 1995;59:1549–55
216. Brown WR, Moody DM, Challa VR, Stump DA, Hammon JW. Longer duration of cardiopulmonary bypass is associated with greater numbers of cerebral microemboli. *Stroke* 2000;31:707–13
217. Ajzan A, Modine T, Punjabi P, Ganeshalingam K, Philips G, Gourlay T. Quantification of fat mobilization in patients undergoing coronary artery revascularization using off-pump and on-pump techniques. *J Extra Corpor Technol* 2006;38:122–9
218. Jewell AE, Akowuah EF, Suvarna SK, Braidley P, Hopkinson D, Cooper G. A prospective randomized comparison of cardiotomy suction and cell saver for recycling shed blood during cardiac surgery. *Eur J Cardiothorac Surg* 2003;23:633–6
219. Brooker RF, Brown WR, Moody DM, Hammon JW Jr, Rebousin DM, Deal DD, Ghazi-Birry HS, Stump DA. Cardiotomy suction: a major source of brain lipid emboli during cardiopulmonary bypass. *Ann Thorac Surg* 1998;65:1651–5
220. Aldea GS, Soltow LO, Chandler WL, Triggs CM, Vocelka CR, Crockett GI, Shin YT, Curtis WE, Verrier ED. Limitation of thrombin generation, platelet activation, and inflammation by elimination of cardiotomy suction in patients undergoing coronary artery bypass grafting treated with heparin-bonded circuits. *J Thorac Cardiovasc Surg* 2002;123:742–55
221. Nuttall GA, Oliver WC, Fass DN, Owen WG, Dinenzo D, Ereth MH, Williams BA, Dearani JA, Schaff HV. A prospective, randomized platelet-function study of heparinized oxygenators and cardiotomy suction. *J Cardiothorac Vasc Anesth* 2006;20:554–61
222. Rubens FD, Boodhwani M, Mesana T, Wozny D, Wells G, Nathan HJ; Cardiotomy Investigators. The cardiotomy trial: a randomized, double-blind study to assess the effect of processing of shed blood during cardiopulmonary bypass on transfusion and neurocognitive function. *Circulation* 2007;116 (11 Suppl):I89–I97
223. Loop F, Szabo J. Events related to microembolism in man during CPB. *Ann Thorac Surg* 1976;21:412–20
224. Paddyachee TS. The effect of arterial line filtration on GME in the middle cerebral arteries. *Ann Thorac Surg* 1988;45:647–49
225. Pugsley W, Klinger, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli on neuropsychological functioning. *Stroke* 1994;25:1393–9
226. Clark RE, Brillman J, Davis DA, Lovell MR, Price TR, Magovern GJ. Microemboli during coronary artery bypass grafting. Genesis and effect on outcome. *J Thorac Cardiovasc Surg* 1995;109:249–57
227. Stump DA, Rogers AT, Hammon JW, Newman SP. Cerebral emboli and cognitive outcome after cardiac surgery. *J Cardiothorac Vasc Anesth* 1996;10:113–8
228. Whitaker DC, Stanton P. The effect of leucocyte-depleting arterial line filters on cerebral microemboli and neuropsychological outcome following CPB. *Eur J Cardiothorac Surg* 2004;25:267–74
229. Riley JB. Arterial line filters ranked for gaseous micro-emboli separation performance: an in vitro study. *J Extra Corpor Technol* 2008;40:21–6
230. Wechsler AS. Consensus statements as a variant of classical statistical methods. *J Thorac Cardiovasc Surg* 2006;132:223