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.

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Total 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.[1,2] 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.[3]

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, Lexigton Kentucky; and ‡Department of Cardiovascular Perfusion, Maine Medical Center, Portland, Maine.

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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.

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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_IIstep6.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.[3] 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.[4] 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.[5] 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.[6,7] The lower limit of cerebral autoregulation may be as low as 20–30 mm Hg in anesthetized patients during hypothermic CPB using moderate hemodilution.[8,9] 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.[10–13] 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.[10–12] Systemic pressures were reduced using lower extremity negative pressure devices and drugs (trimethaphan or labatolol) 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.[13] 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[14–16] or unchanged[17–19] 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.[20] 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.[21] A subsequent analysis of the same database revealed an association between lower MAPs and less neurologic injury.[22] 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.[23] 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.[24] 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.[25]

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.[26] 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 ± 7 mm Hg) than the targeted pressure, while in the low pressure group the achieved pressure (52 ± 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.[27] 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_2)
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.[28] 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,[27] the elderly (cognitive decline has been associated with lower MAPs in older patients),[29] hypertensive patients (cerebral autoregulation curve shifted to the right),[30] and patients with diabetes (abnormal cerebral autoregulation during CPB).[31]

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 (2.2–2.5 $L \cdot min^{-1} \cdot m^{-2}$) approximates the cardiac index of a normothermic anesthetized patient with a normal hematocrit.[32] However, perfusion flows as low as 1.2 $L \cdot min^{-1} \cdot m^{-2}$ during hypothermic bypass have been used by some investigators with good clinical outcomes.[9,33] 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 1.0–2.4 $L \cdot min^{-1} \cdot m^{-2}$ when hypothermic bypass was used,[9,32,33], Table 4. In contrast, Soma et al. observed that CBF increased proportionally to the CPB pump flow under conditions of moderate hypothermia.[34] 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[35,36] or resulted in decreased CBF when flows were reduced.[37,38] 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 $mL \cdot kg^{-1} \cdot min^{-1}$) and low (50 $mL \cdot kg^{-1} \cdot min^{-1}$) pump flows in rabbits.[39] 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.[40] Increasing the pump flow restored perfusion to the pancreas, colon, and kidneys, whereas restoration of systemic pressures with phenylepherine did not. Using a similar animal model, Mackay et al. reduced pump flows to achieve a systemic pressure of 45 mm Hg.[41] 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 (30–50 $mL \cdot kg^{-1} \cdot min^{-1}$), low-pressure (30–60 mm Hg) CPB.[42] Ellis et al. also observed a low incidence of neurocognitive dysfunction (17%) in 30 patients undergoing hypothermic (28°C) bypass at flow rates <40 $mL \cdot kg^{-1} \cdot min^{-1}$.[17] 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[32]	30	1.2–2.3 $L \cdot min^{-1} \cdot m^{-2}$	27°C	α stat	50–70	No differences in mean CBF or CMR at high or low flows
Govier et al., 1984[9]	67	1.0–2.2 $L \cdot min^{-1} \cdot m^{-2}$	27°C	α stat	45–70	No change in regional CBF or CMR at differing flow rates
Rogers et al., 1992[33]	24	1.75–2.25 $L \cdot min^{-1} \cdot m^{-2}$	27°C	α stat and pH stat	68–75	No difference in CBF or CMR at differing flow rates
Soma et al., 1989[34]	21	40–70mL $\cdot kg^{-1} \cdot min^{-1}$	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.

$L \cdot min^{-1} \cdot m^{-2}$) and adverse renal and neurologic outcomes in a prospective observational study.[20] 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_2 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.[43–45] 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.[46–49] However, recent large databased investigations have described an association between lowest hematocrit on bypass and postoperative morbidity and mortality,[50–59] (Table 5). DeFoe et al. observed a strong inverse relationship between hematocrit levels on bypass and in-hospital mortality, need for intraaortic balloon pump support, and return to bypass after attempted separation.[50] 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.[51] Both studies identified trends towards increased morbidity and mortality at all hematocrits below 22% to 23%.[50,51] Other large databased investigations have observed that lowest hematocrit on bypass was an independent risk factor for renal[52–54] and neurologic injury.[57] Karkouti et al. observed a 10% increased risk of stroke rate with each percent decrease in the nadir hematocrit,[57] (Fig. 1). Mathew et al. observed a higher incidence of neurocognitive decline in elderly patients randomized to receive profound hemodilution (hematocrit of 15%–18%).[58] 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.[52,53,56] 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.[59] 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.[43] 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[50]	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[51]	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[55]	2738	In-hospital mortality	14% all patients 17% high-risk patients	Lowest Hct associated with increased mortality
Karkouti et al., 2005[52]	9080	ARF requiring dialysis	<21% or >25%	Hct values <21% or >25% associated with increased risk of ARF
Habib et al., 2005[53]	1760	Charge in serum creatinine ARF	24%	Lowest Hct on CPB associated with increased risk of creatinine rise and ARF
Swaminathan et al., 2003[54]	1404	Change in serum creatinine	None identified	Lowest Hct associated with creatinine rise
Ranucci et al., 2006[56]	1766	In-hospital mortality morbidity	23%	Lowest Hct associated with cardiac low output syndrome and ARF
Karkouti et al., 2005[57]	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.

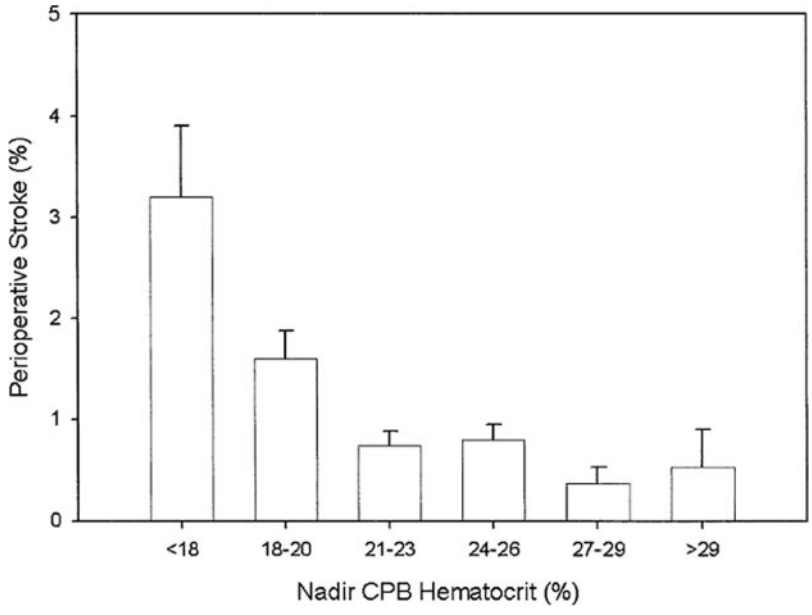

Figure 1. The unadjusted relationship between lowest hematocrit on cardiopulmonary bypass (categorized into six groups) and risk of perioperative stroke. Reprinted with permission from Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeysundera D, Ivanov J, Karski J. Low hematocrit during cardiopulmonary 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.[44] 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,[60,61] mediastinitis,[62] and hospital length of stay.[63]

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.[53,56] 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 DO_2 during CPB may be one of the most important determinants of "optimal" perfusion. DO_2 is calculated by multiplying the pump flow rate by the arterial oxygen content:

DO_2 = pump flow × ((hemoglobin concentration × hemoglobin saturation × 1.36) + (0.003 × arterial oxygen tension)).

The 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, 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 [F_{IO_2}]).

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 $L \cdot min^{-1} \cdot m^{-2}$. Assuming normoxia and a hemoglobin of 12 g/dL, this results in a DO_2 of approximately 350–450 $mL \cdot min^{-1} \cdot m^{-2}$.[64] During CPB, if flows of 2.2 to 2.4 $L \cdot min^{-1} \cdot m^{-2}$ are maintained and hemoglobin values decrease to 7 to 8 g/dL, DO_2 will be reduced to 200–300 $mL \cdot min^{-1} \cdot m^{-2}$. The reduction in 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 (VO_2) is unchanged, an increase in the oxygen extraction ratio is required to compensate for the reduced DO_2. Therefore, the safe margin between oxygen supply and demand may be narrowed during CPB.

The minimal safe DO_2 during bypass, termed the critical DO_2, has been assessed in several investigations. As DO_2 decreases, 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 VO_2 and tissue oxygenation begin to decrease and metabolic (lactic) acidosis begins to develop ("flow dependent oxygen consumption") (Fig. 2). The critical DO_2 in anesthetized humans without CPB has been claimed to be approximately 330 $mL \cdot min^{-1} \cdot m^{-2}$.[65,66]

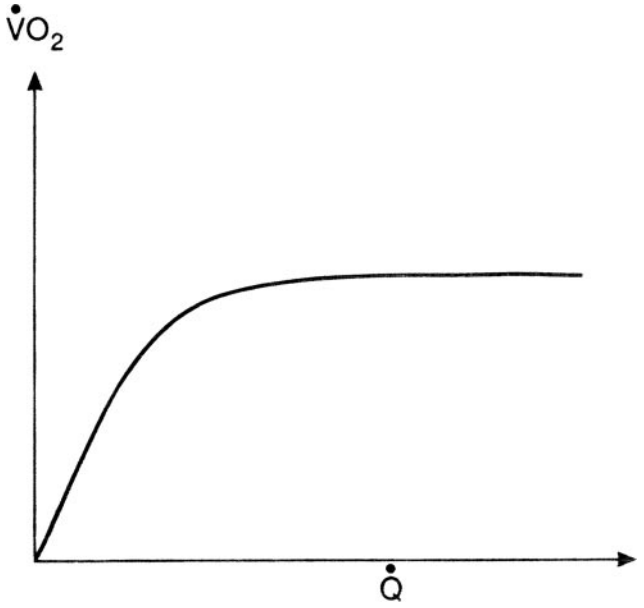

Figure 2. Relationship between oxygen delivery (DO_2) and consumption (VO_2). As flow (Q) or DO_2 decreases, oxygen extraction ratio increases and VO_2 remains stable and independent of DO_2. At the knee of the curve, oxygen extraction is maximal, and flows below this critical DO_2 value result in tissue hypoxia.

Critical DO_2 values during CPB have not been definitively established. Studies in cardiac surgical patients have examined the relationship between DO_2 and VO_2. Some investigations have identified a DO_2 level below which VO_2 values begin to decrease (critical DO_2 of 280–300 $mL \cdot min^{-1} \cdot m^{-2}$).[67,68] In contrast, other investigators have observed a direct linear relationship between DO_2 and VO_2 during CPB, and have been unable to determine a critical DO_2 value.[69]

The effects of alterations in pump flow, F_{IO_2} and hematocrit concentrations on DO_2 (and VO_2) have been assessed in several investigations. In patients undergoing hypothermic CPB, reductions in pump flows to <1.2–1.5 $L \cdot min^{-1} \cdot m^{-2}$ resulted in decreases in VO_2, suggesting that DO_2 is compromised at flows below these values.[70,71] In contrast, VO_2 was unchanged when DO_2 was significantly decreased by reducing flow to as low as 1.2 $L \cdot min^{-1} \cdot m^{-2}$.[72,73] Increasing the F_{IO_2} will improve DO_2 during and after CPB. The influence of 100% F_{IO_2} on tissue oxygen tension is less certain, with studies in cardiac surgical patients demonstrating improved[74] and worsened[75] skeletal muscle oxygen tension during hyperoxia. Similarly, transfusion of PRBCs will increase systemic DO_2, yet may not improve oxygenation at the tissue level.[74] 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 VO_2 and DO_2 has not been established. In low-risk CABG patients, hemodilution to a hematocrit of 20% during normothermic bypass

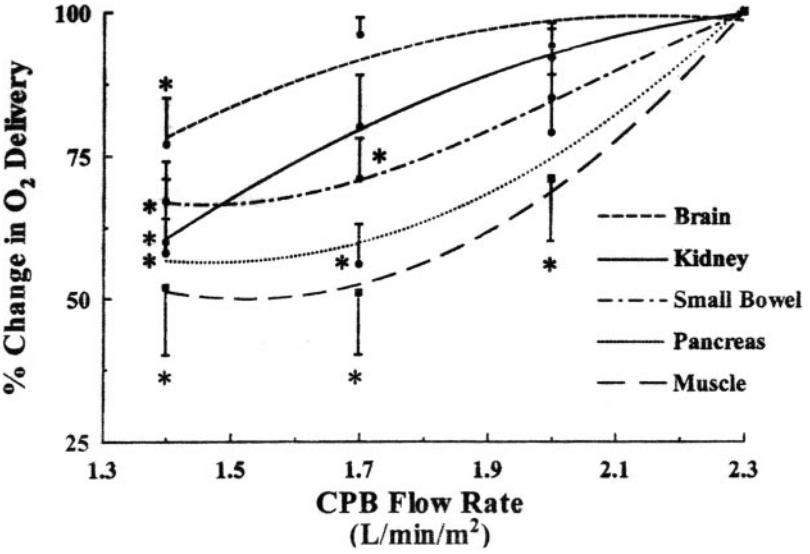

Figure 3. Changes in regional oxygen delivery at varying bypass flow rates. Oxygen delivery to the brain and kidneys was relatively well maintained at flows more than 1.4 $L \cdot min^{-1} \cdot m^{-2}$. However, oxygen delivery to muscle and visceral organs was significantly reduced at higher flow rates (1.7–2.0 $L \cdot min^{-1} \cdot m^{-2}$). 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 DO_2 (DO_2 was maintained above a "critical" value of 330 $mL \cdot min^{-1} \cdot m^{-2}$) or compromise clinical outcomes.[76] In a dog model of normothermic bypass, DO_2 and VO_2 were maintained at hematocrits between 39% and 25%.[77] Significant decreases in both values occurred when hematocrits were reduced to 18% or less.

The delivery of an acceptable whole-body DO_2 does not ensure that DO_2 to all organ beds is maintained. An organ-specific hierarchy of DO_2 during CPB has been observed. During normothermic bypass in pigs, DO_2 to the brain was maintained at baseline levels at pump flows of 1.4 to 2.3 $L \cdot min^{-1} \cdot m^{-2}$[78] (Fig. 3). In contrast, DO_2 significantly decreased to the kidneys, pancreas, and muscle beds at all flow rates studied (Fig. 3). These findings suggest that DO_2 to the brain may be preserved at the expense of DO_2 to other organ systems. In a similar animal model, significant decreases in mesenteric DO_2 and progressive increases in mesenteric VO_2 were observed during 120 min of normothermic bypass at 100 $mL \cdot min^{-1} \cdot m^{-2}$.[79] A 21% decrease in splanchnic DO_2 has been noted in patients during moderate hypothermic bypass at standard pump flows of 2.1–2.2 $mL \cdot min^{-1} \cdot m^{-2}$.[80] The use of higher pump flow rates (>2.4 $L \cdot min^{-1} \cdot m^{-2}$) during normothermic bypass has been demonstrated to maintain splanchnic DO_2 at baseline values.[81] 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 (2.5–2.7 $L \cdot min^{-1} \cdot m^{-2}$) to maintain the DO_2 at pre-CPB levels.[82]

Some insight about the impact of DO_2 on outcomes may be derived from a prospective observational study examining the role of DO_2 during bypass on postoperative renal dysfunction.[83] In a cohort of 1048 CABG patients, Ranucci et al. investigated the association between lowest DO_2, hematocrit, and pump flow on bypass and the development of postoperative renal dysfunction.[83] The best predictor for acute renal failure and peak postoperative serum creatinine levels was the lowest DO_2 on bypass, with a critical value of 272 $mL \cdot min^{-1} \cdot m^{-2}$. The authors concluded that targeting 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.[84,85] Although hypothermia effectively reduces overall VO_2, the balance between oxygen supply and demand can be impaired by reductions in tissue 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°–37°C) or cold (25°–30°C) bypass.[86] In contrast, investigators from Emory observed a significantly higher incidence of stoke and encephalopathy (4.5% vs 1.4%) in patients

randomized to normothermic (≥35°C) bypass compared to moderate hypothermic (≤28°C) bypass.[87] 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.[88]

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

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.[97] A substudy of 300 patients randomized to warm or hypothermic bypass revealed no differences in postoperative creatinine clearance between groups.[98] In two small studies of warm versus hypothermic bypass, platelet function was significantly more impaired in patients randomized to hypothermia.[99,100] However, fibrinolytic activity may be greater at warmer temperatures.[101] 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°C or 25°C.[102] Studies not specifically designed to examine hematologic outcomes have observed that bleeding and transfusions were higher in hypothermic groups[89,92,103] or not different between temperature groups.[91]

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.[88] 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.[104]" 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°C versus 37°C) were both associated with a reduced incidence of postoperative neurocognitive dysfunction.[105–107] Limiting arterial line temperature to 37°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 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.[108] 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[109]	Taylor KM et al., 1982[110]
Myocardial infraction	Murkin JM et al., 1995[109]	Abramov D et al., 2003[111]
Requirement for mechanical or pharmacologic circulatory support	Song Z et al., 1997[112] Taylor KM et al., 1982[110] Murkin JM et al., 1995[109]	
Neurologic injury (stroke or neurocognitive dysfunction)	Takahara Y et al., 2000[113]	Murkin JM et al., 1995[114] Henze T 1990[115] Abramov D et al., 2003[111]
Renal injury	Kocakulak M et al., 2005[116] Abramov D et al., 2003[111]	Badner NH et al., 1992[117]
Splanchnic perfusion	Hamulu A et al., 1998[118] Gaer JA et al., 1994[119]	Mathie RT et al., 1997[120]
Inflammatory mediator release	Sezai A et al., 2005[121] Driessen JJ et al., 1995[122]	Dapper F et al., 1992[123]
Release of endogenous vasoactive mediators (catacholamines, plasma renin)	Zamparelli R et al., 2000[124] Sezai A et al., 2005[121] Canivet JL et al., 1990[125]	Goto M et al., 1993[126]

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[109] or unaffected[110,111] 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.[112–120] 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.[121–126] 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.[127]

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.[128,129] 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%.[130] In addition, the hemodynamic energy delivered by currently approved pulsatile pumps is significantly less than normal physiologic pulsatility.[131] 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.[132] The design of the aortic cannula can also affect the pulsatile waveform morphology.[133] 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 $Paco_2$ Management

The influence of acid-base management during CPB on outcomes has been recently reviewed in this journal.[134] Although basic science and clinical studies have demonstrated physiologic advantages to both α-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

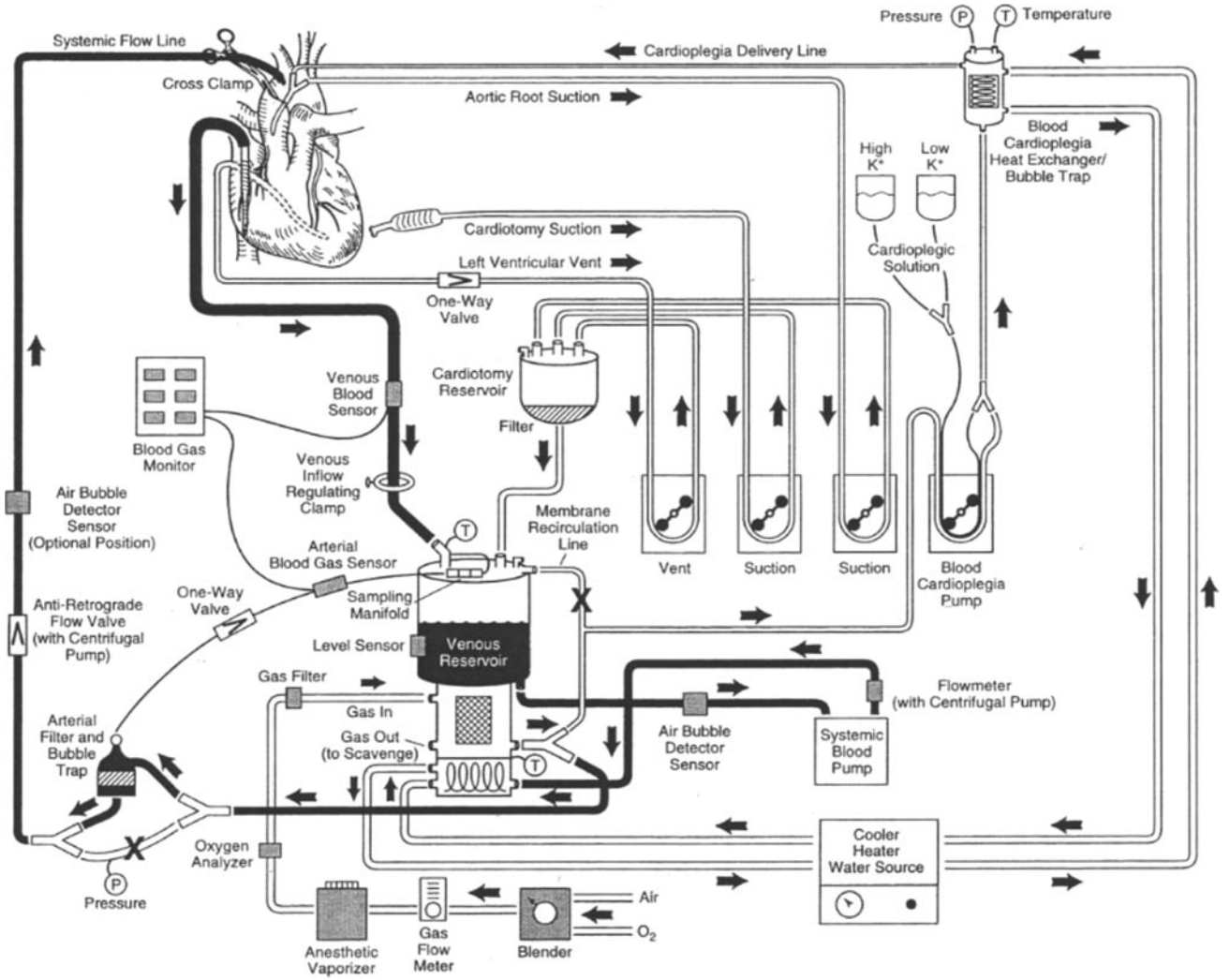

Figure 4. Schematic diagram of typical cardiopulmonary bypass circuit displaying the components discussed in this review. Illustrated are the systemic blood pump (lower right), oxygenator and venous reservoir (incorporated as a single hard-shell unit which also includes the heat-exchanger, depicted in the lower center of this diagram), cardiotomy 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

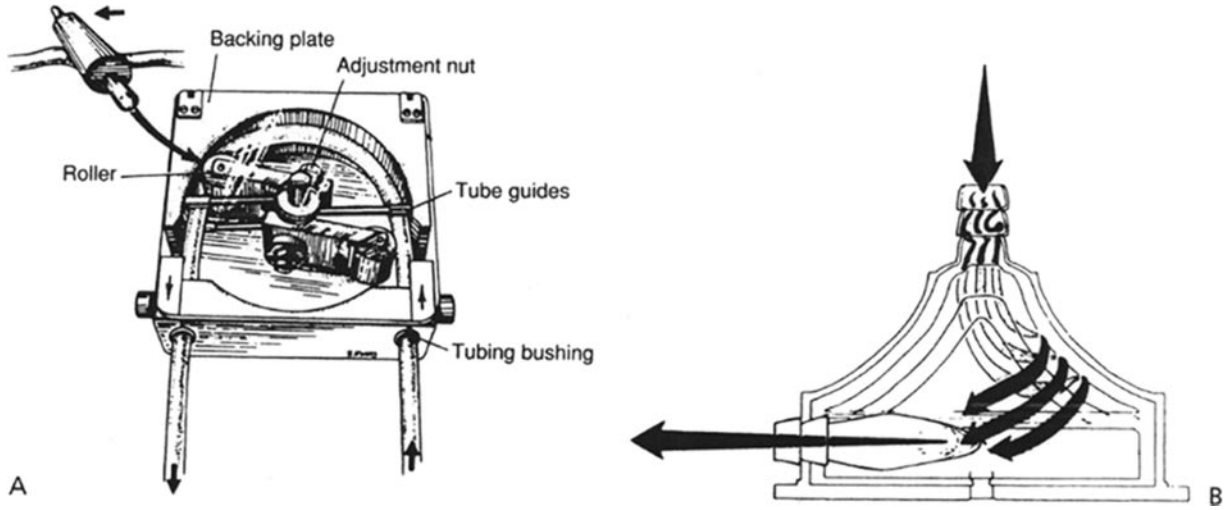

Figure 5. Arterial Blood Pumps: (A) Roller Pump-Plastic ("pump head") tubing rests inside the race-way. The rollers mounted on arms 180 degrees apart nearly occlude the tubing and act like a rolling pin, squeezing the blood ahead of it and out the pump. It is insensitive to afterload. (B) Centrifugal 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.[135] 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.[136] Studies of tubing wear over time have shown that polyvinylchloride fragments generated from roller pumps are numerous, frequently <20 μm in diameter, and begin to occur during the first hour of use.[137]

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.[138] 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.[139–148] Several studies reported less hemolysis with the centrifugal pump when tested *in vitro*.[139–142] 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.[144] Rawn et al. compared an underocclusive 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).[145] 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,[149–170] (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.[149] 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.[150] Rates of hemolysis have been compared in seven randomized clinical trials. Two reported greater hemolysis with roller pumps,[161,168] one observed greater evidence of hemolysis with a centrifugal

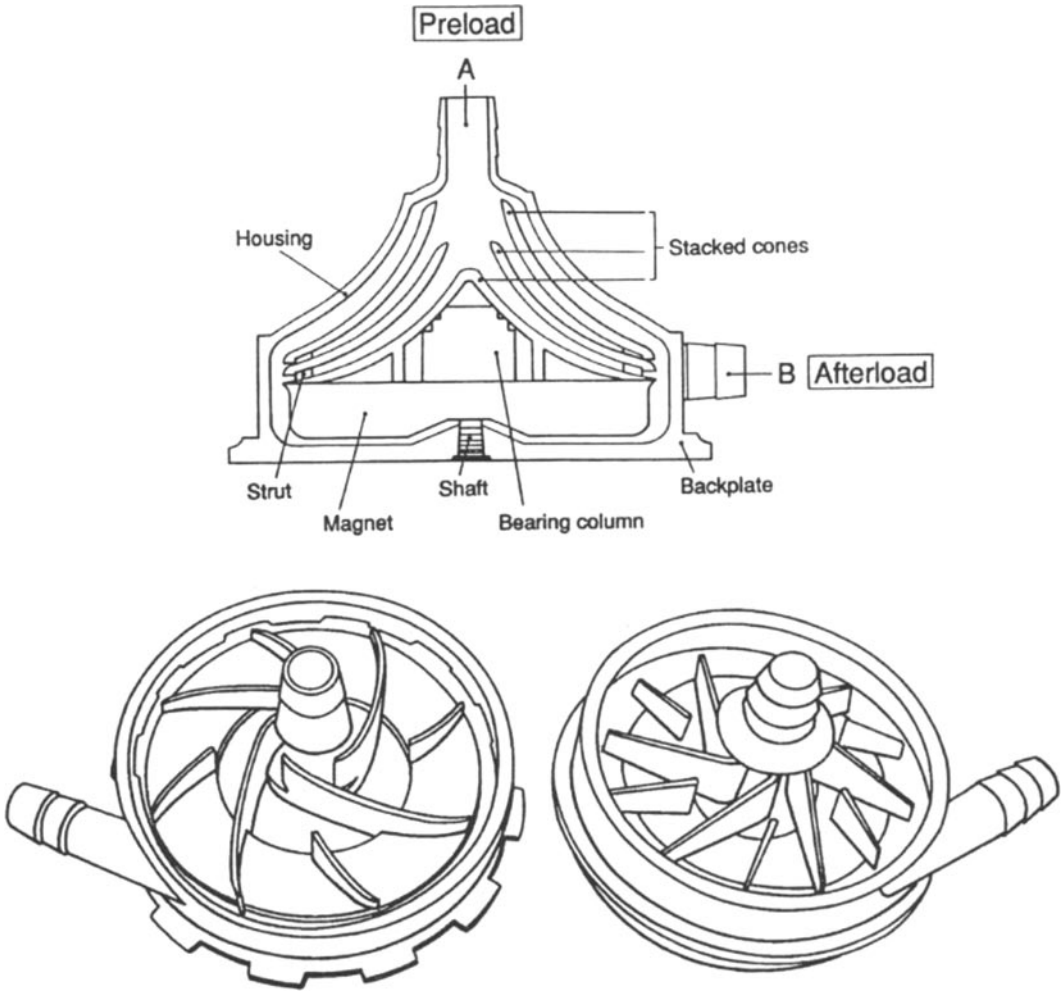

Figure 6. Centrifugal Blood Pump: (A) plastic cone(s) or impeller is mounted inside the conical plastic housing. The impeller is rotated by the motor outside and beneath the base of the plastic housing (magnetic coupling). The difference of the velocity (centimeters per second) of the narrow potion of the impeller cone (at the top) as compared with the wider potion 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,[149] and four found no difference between the two types of pumps.[151,152,163,167] 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%.[157] Randomized trials with neurologic measures as a primary outcome variable, however, have not demonstrated significant differences in neuropsychologic outcomes or S100 β levels between types of pump.[153,155] In the largest randomized trial, Klein et al. assigned 1000 adult cardiac patients to management with a roller pump or a centrifugal pump.[152] 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).[160–163] 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).[171] In 2000, approximately 50% of the cardiac centers in the United States routinely used centrifugal pumps.[172]

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.[173] 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.[174–178] *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.[179–204] Most investigations have shown evidence of reduced platelet activation,[183–186] attenuation of inflammatory processes,[187–194] and improvement in clinical outcomes (bleeding and transfusions,[195–197] pulmonary function,[198,199] and cognitive outcomes[200–202]).

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 cardiotomy 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.[171,179] 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.[179] 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.[205] 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)[171]" and that "reduction of circuit surface and the use of biocompatable surface-modifed circuits might be useful–effective in reducing the systemic inflammatory response (Class IIa-Level of Evidence B).[206]"

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.[207]

Numerous studies have identified the occurrence of gaseous microemboli (GME) during cardiac surgery with CPB.[208–211] 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.[212–214] In addition, commonly used microporous membrane oxygenators have widely variable characteristics related to how they handle gas.[212,213] 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 cardiotomy 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 cardiotomy reservoir and addition of a separate reservoir is required if cardiotomy 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,

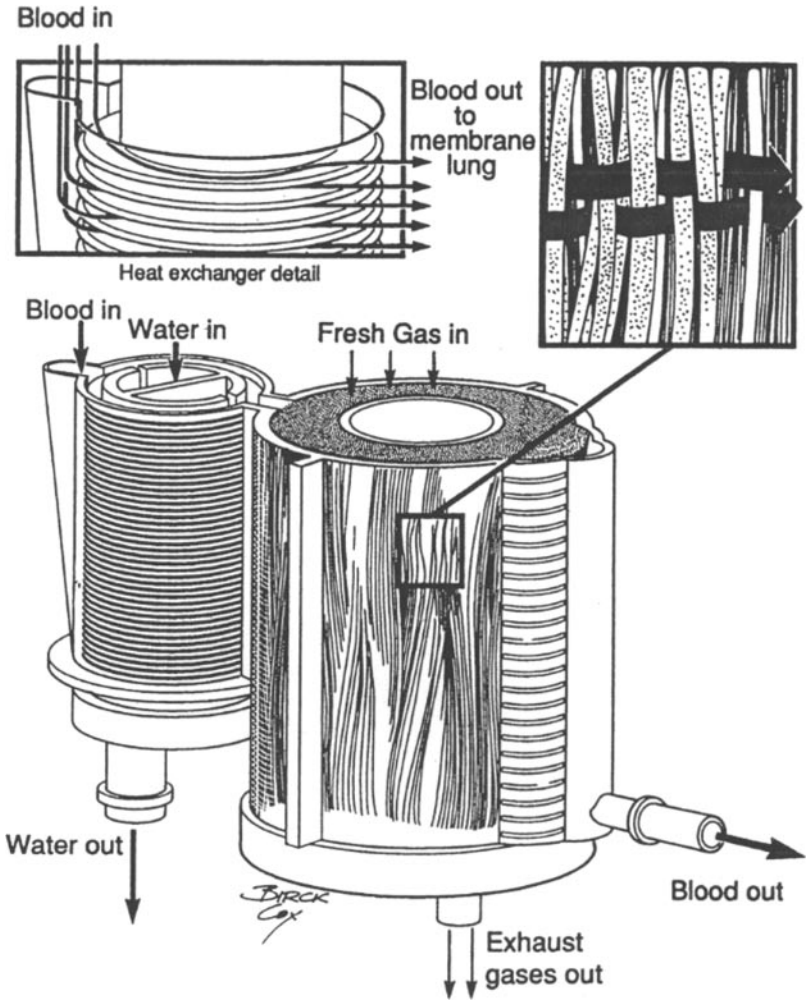

Figure 7. Hollow fiber microporous membrane oxygenator. The oxygenator contains multiple bundles of hollow fibers. "Ventilating" gas (oxygen, air, volatile anesthetic agents, ± carbon dioxide) is passed through the inside of the hollow fibers, while the venous return blood is passed around the hollow 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 Wlliams & 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 compliment activation and release of polymorphoneculocytes elastase has been observed with the use of a closed system.[169] Schönberger et al. prospectively studied differences in inflammatory and coagulation activation of blood in cardiac patients treated with open and closed reservoir systems.[215] 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).[171]

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, Cardiotomy Suction vs Closed Venous Reservoirs

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

RCT = Randomized controlled trial: HC = heparin-coated; NHC = not heparin-coated; RP = roller pump; CP = centrifugal pump; OR = open reservoir; CR = closed reservoir; CS = cardiotomy suction; CARD = cardiotomy suction system; NCARD = no cardiotomy 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.[216] For each 1-h increase in the duration of CPB, the embolic load increased by 90.5%. Cardiotomy suction blood has been identified as a major source of lipid emboli in several studies.[217–219]

For this reason, some have advocated eliminating the use of cardiotomy suction which is returned directly to the ECC. Several clinical studies have examined the effects of eliminating cardiotomy suction (Table 7). In a randomized trial enrolling CABG patients, use of cardiotomy suction resulted in significant increases in thrombin generation, neutrophil and platelet activation, as well as the release of neuron-specific enolase.[220] Nuttall et al., in a study of patients in whom an open venous reservoir was used, compared the return of cardiotomy suction directly to the ECC, versus sequestration and processing of cardiotomy blood to a cell saver.[221] 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 cardiotomy suction blood (control group) to that processed by centrifugal cell washing followed by lipid filtration (treatment group).[222] 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 cardiotomy 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.[223,224] Some studies suggest that 20-μm filtration is superior to 40-μm filtration in the reduction of cerebral embolic counts.[224] 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.[225–227] 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.[228] The GME separation performance of 10 different arterial line filters in clinical use has been recently evaluated.[229] 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 of evidence supporting this practice was high (Class I-Level of Evidence A).[206]

Table 8. Recommendation for the Practice of Cardiopulmonary Bypass by Shann et al., 2006[206]

1. The clinical team should manage adult patients undergoing moderate hypothermic CPB with alpha stat pH management (Class 1, 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)

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.[230] At least three such documents have been recently published which relate to CPB[134,171,206] Hogue et al. provided an evidenced-based appraisal of current practice of CPB on neurologic outcome which was recently published in this journal[134] 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.[206] (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)[171]

1. During cardiopulmonary bypass with moderate hypothermia, transfusion of red cells for a hemoglobin ≤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_2, 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 ≥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.[171] 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.

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