Con: During Cardiopulmonary Bypass for Elective Coronary Artery Bypass Grafting, Perfusion Pressure Should *Not* Routinely Be Greater Than 70 mmHg

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WITHIN THE SPAN OF 50 years, cardiopulmonary bypass (CPB) has been transformed from an uncommon hazardous technique to a sophisticated, everyday occurrence. However, questions regarding the fundamental management of bypass remain unanswered: What is the optimum temperature management strategy during CPB? What is the optimum pump flow? Is pulsatile blood flow more physiologic during CPB? What is the optimum perfusion pressure during CPB?

Answering these questions is critical to reducing the substantial incidence of postoperative neurologic dysfunction that occurs after CPB. This incidence may be as high as 6%[1] for gross neurologic injury or 57%[2] for mild cognitive changes. The cause of postoperative neurologic dysfunction is not fully understood, but is believed to be a result of both embolic phenomena and hypoperfusion during CPB. The ideal perfusion pressure therefore represents a careful balance of risks. Reduced perfusion pressure and blood flow may decrease cerebral embolic load but increase the risk of hypoperfusion, whereas elevated perfusion pressures and flow may decrease the likelihood of hypoperfusion but increase cerebral embolic load. Although the ideal perfusion pressure has not yet been defined, using the lowest perfusion pressure that does not risk hypoperfusion would seem logical. This ideal or routine perfusion pressure is the subject of considerable debate, and the focus of this article.

Cerebral autoregulation maintains a relatively constant blood flow for mean arterial blood pressure between 50 and 150 mmHg, assuming other physiologic variables remain constant (Table 1). During hypothermic CPB, the lower limit of cerebral autoregulation reaches 20 to 30 mmHg.[3,4] Because cerebral autoregulation is left-shifted during hypothermic CPB, hypoperfusion would not be expected to occur unless perfusion pressure was significantly less than 50 mmHg, and routine CPB perfusion pressure near 50 mmHg would appear to be safe.

The routine use of higher perfusion pressure ($\geq$70 mmHg) may lead to worse neurologic outcome. The evidence is as follows. During alpha-stat acid-base management, the pressure-flow autoregulatory plateau has a slightly positive slope,[5] so that increasing perfusion pressure increases cerebral blood flow[6,7] and thus increases embolic load. These phenomena lead to an increased incidence of adverse neurologic outcomes.[8] Increased cerebral blood flow associated with increased adverse neurologic events is also seen during pH-stat acid-base management.[3,9]

In addition to neurologic complications, higher perfusion pressures ($\geq$70 mmHg) may be associated with other adverse events. Increased pressure and blood flow may cause greater trauma to blood elements, exacerbate the inflammatory process associated with CPB, and reduce the effectiveness of circulating blood elements. Finally, excessively high perfusion pressure during CPB greatly compromises one of the primary imperatives of bypass, the opportunity for the surgeon to operate on a still heart in a bloodless field. Although it would be difficult, if not impossible, to quantify the effect of a blood-filled versus bloodless field on the long-term patency of coronary anastomoses, clinicians should carefully consider the opinion offered by Dr Norman Shumway: "The most important predictor of long-term outcome is the surgeon's ability to complete the coronary anastomoses." (Personal communication, 1992.)

Of all the adverse events potentially associated with perfusion pressure management during CPB, neurologic outcome has received the most attention. Early studies[10-13] found severe hypotension during CPB was associated with postoperative neurologic deficits, highlighting the potential role of hypoperfusion in postoperative neurologic dysfunction. However, the magnitude and duration of hypotension in these studies were not well quantified. Stockard et al[14] helped to correct this deficit by establishing the concept of tm^{50} (the integral of perfusion pressure $\leq$ 50 mmHg over time). The subsequent study by Stockard et al[15] of 75 cardiac surgical patients reported a 53% incidence of postoperative central nervous system dysfunction in patients who experienced an integrated hypotensive time of 100 mmHg · min or greater versus a 10% incidence of postoperative central nervous system dysfunction in those who did not suffer this magnitude of hypotension. However, tm^{50} or other measures of hypotension (equivalent to perfusion pressure $\leq$ 50 mmHg) do not consistently predict postoperative neurologic deficits (Table 2). For example, Slogoff et al,[16] in a prospective study of 204 patients, found perfusion pressures of 50 mmHg or less during CPB were not associated with an increase in the likelihood of postoperative cerebral dysfunction. In a subsequent study,[17] neither the value of the lowest measured blood pressure nor integrated hypotension was predictive of postoperative neurologic dysfunction.

Additional studies have both supported[18-20] and refuted[4,21-30] the relationship between intraoperative hypotension and postoperative neurologic dysfunction (Table 2). Direct comparison of these studies is difficult because outcomes are reported differently (neurologic *v* neuropsychologic), CPB management techniques have evolved over the last 30 years (eg, pH *v* alpha-stat acid-base management, use of arterial filters, etc), and study designs vary (retrospective *v* prospective). Most of the studies that suggested an association between hypotension and worsening neurologic outcome have used 50 mmHg as the limit for defining hypotension. Because of this, 50 mmHg has become a common, if not routine, lower limit for perfusion pressure during CPB, despite a substantial amount of conflicting data.

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Table 1. Variables Affecting Cerebral Blood Flow

Cerebral metabolic rate
$PaCO_2$
PaO_2
Blood viscosity
Intracranial pressure
Mean arterial pressure
Central venous pressure
Anesthetics/sedative-hypnotics

NOTE. Cerebral blood flow variables are reviewed by Schell et al.[33]

Gold[31] addressed many of the limitations of previous studies (Table 2) by using a prospective, randomized, controlled study design. He randomized 248 patients to either high (80 to 100 mmHg) or low (50 to 60 mmHg) perfusion pressures during CPB. Vasoactive drugs were administered to achieve these blood pressure endpoints. Fewer combined (cardiac and neurologic) adverse outcomes were noted in the high–perfusion-pressure group (4.8%) than the low–perfusion-pressure group (12.9%). However, the incidence of either cardiac or neurologic adverse events did not vary between the high- or low-pressure groups when considered independently. The suggested trend toward more cardiac complications in the low–perfusion-pressure group ($p = 0.3$) may be explained by the fact that this group suffered more preoperative cardiac dysfunction (greater nitrate use, $p = 0.007$) and had a greater incidence of angina, $p = 0.008$). The trend ($p = 0.076$) toward a greater number of neurologic complications in the low–perfusion-pressure group (50 to 60 mmHg) merits further consideration.

One explanation for this trend is a difference in the prevalence of preexisting cerebrovascular disease in the two treatment groups. Evidence for this comes from a later publication by the same investigators reporting on atheroma grade in the descending aorta of 189 of the 248 original study participants.[32] Severe atheromatous disease in the descending aorta is likely a marker for the presence of cerebrovascular or aortic arch disease. Given this, 10 of 88 participants in the high-pressure group had the more severe grades (IV or V) of atheromatous disease compared with 20 of 101 participants in the low-pressure group. These differences suggest that the greater incidence of preexisting cerebrovascular or aortic arch disease in the low-pressure group was responsible for the greater incidence of adverse neurologic outcomes. Alternatively, higher perfusion pressures may reduce adverse neurologic events, but only in patients with more advanced atherosclerotic disease. Indeed, if patients with the worst atheromatous disease (grade V) are removed from the analysis, the trend toward worse neurologic outcomes in the lower perfusion pressure group is lost ($p = 0.281$ *v* $p = 0.076$; Table 3). In summary, higher perfusion pressure (80 to 100 mmHg) in the study by Gold et al[31] does not appear to improve neurologic outcome in all patients, although it may improve neurologic outcome in patients with severe atherosclerotic disease (aortic arch or cerebrovascular).

Table 2. Intraoperative Hypotension as a Risk Factor for Worse Neurologic or Neuropsychologic Outcome

Refuting Studies		Supporting Studies	
Reference	No. of Patients	Reference	No. of Patients
Kolkka and Hilberman[28] (1980)	204	Gilman[10] (1965)	35
Ellis et al[22] (1980)	30	Javid et al[11] (1969)	100
Sotaniemi et al[27] (1981)	49	Tufo et al[12] (1970)	100
Slogoff et al[16] (1982)	204	Lee et al[13] (1971)	71
Govier et al[4] (1984)	67	Stockard et al[14] (1973)	25
Nussmeier et al[26] (1986)	182	Stockard et al[15] (1974)	75
Fish et al[25] (1987)	100	Brainthwaite et al[20] (1975)	538
Townes et al[24] (1989)	90	Savageau et al[18] (1982)	227
Slogoff et al[17] (1990)	504	Gardner et al[19] (1985)	168
Bashein et al[21] (1990)	86	Gold et al[31] (1995)	248
Stanley et al[29] (1990)	19		
Kramer et al[30] (1994)	230		
McKhann et al[23] (1997)	456		

In addition to patients with advanced atherosclerotic disease (cerebrovascular or aortic arch), three other groups may benefit from increased perfusion pressures during CPB: the elderly, diabetics, and those with chronic hypertension.

Many reports have identified advanced age as a risk factor for adverse neurologic outcomes after CPB.[33] Initially, it was believed that the elderly had impaired cerebral autoregulation and were thus more vulnerable to cerebral injury during bypass. However, Newman et al[34] found no affect of age on cerebral autoregulation (either cerebral perfusion pressure-blood flow or cerebral metabolism-flow coupling), although elderly patients tended to have a greater difference in arterial and venous blood oxygen content. In a subsequent study, mean arterial pressure less than 50 mmHg and rapid rewarming were associated with decline in one of five tests of cognitive function.[35] These two studies do not permit determination of whether the higher rate of cognitive dysfunction in the elderly is because of hypoperfusion or a greater sensitivity to embolic load. Interestingly, in the first study,[34] correlation was found between cerebral arterial-venous blood oxygen content difference and five of nine tests of cognitive function. Increased cerebral dysfunction in the elderly may be a result of slower vasodilatation of cerebral resistance vessels during periods of rewarming and subsequent transient episodes of metabolism-flow mismatch with resultant ischemia. It is unknown what the effect of elevating perfusion pressure during rewarming would be on neurologic outcome. To date, there are insufficient data to support using elevated perfusion pressures in the elderly who do not have advanced atherosclerotic disease or chronic hypertension.

Hypertensive patients are generally accepted to have intact

Table 3. Patient Outcome Versus Perfusion Pressure

Targeted Perfusion Pressure During CPB (mmHg)	Patients With Neurologic Complication	Patients Without Neurologic Complication
50-60	9 (5)	115 (113)
80-100	3* (2†)	121 (117)

NOTE. *$p = 0.076$, chi-squared.

†$p = 0.281$, Fisher's two-tailed exact test. Data from[31] are only available on 189 of 248 patients in original study. Numbers in parentheses reflect removal of all subjects who had grade V atheroma of the descending aorta, by their outcome classification[32] (stroke or no stroke).

pressure-flow autoregulation[33] with a right shift; therefore, pressure-dependent flow patterns may develop at higher perfusion pressures than in the normal population. In hypertensive patients, the use of higher perfusion pressures during CPB is already in common practice.

Patients with type I diabetes mellitus appear to have impaired metabolism-flow coupling during CPB.[36] They also have some loss of pressure-flow autoregulation, although it is unclear if this slightly positive slope is any different from that reported for nondiabetics.[5] Because of this, the primary risk period of neurologic injury for patients with diabetes would likely be during periods of rapid rewarming or normothermia in which cerebrovasodilation may not meet metabolic needs. The role of higher perfusion pressure during these periods, as in the case of bypass management for the elderly, is of uncertain but potential benefit.

To summarize, CPB continues to be associated with an unacceptable incidence of adverse neurologic events. The cause of these complications is likely a combination of embolic phenomena and hypoperfusion. Whereas elevated perfusion pressures during CPB (>70 mmHg) may help decrease the incidence of hypoperfusion in some patient groups, this beneficial effect may be offset by increased embolic loads, bleeding complications, and compromised myocardial protection and operating conditions. Before becoming routine practice, patient groups who benefit will need to be differentiated from those harmed by higher perfusion pressure. To date, this appears to be patients with severe atherosclerotic disease (aortic arch or cerebrovascular) or chronic hypertension. Patients who have diabetes or are elderly are at higher risk for adverse neurologic outcome, but whether they will benefit or suffer from the use of higher perfusion pressure during CPB is unknown. Likewise, the optimum perfusion pressure for the remaining patient population has yet to be determined. Currently, there is no rationale for the routine use of perfusion pressures greater than 70 mmHg.

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