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Relationship between Cardiopulmonary Bypass Flow Rate and Cerebral Embolization in Dogs

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Background: **Cerebral embolization is a primary cause of cardiac surgical neurologic morbidity. During cardiopulmonary bypass (CPB), there are well-defined periods of embolic risk. In theory, cerebral embolization might be reduced by an increase in pump flow during these periods. The purpose of this study was to determine the CPB flow–embolization relation in a canine model.**

Methods: **Twenty mongrel dogs underwent CPB at 35°C with α-stat management and a fentanyl–midazolam anesthetic. In each animal, CPB flow was adjusted to achieve a mean arterial pressure of 65–75 mmHg. During CPB, an embolic load of 1.2×10^5 67 μm fluorescent microspheres was injected into the arterial inflow line. Before and after embolization, cerebral blood flow was determined using 15-μm microspheres. Tissue was taken from 12 brain regions and microspheres were recovered. The relation between pump flow and embolization/g of brain was determined.**

Results: **The mean arterial pressure at embolization was 67 ± 4 mmHg, and the range of pump flow was 0.9–3.5 $l \cdot min^{-1} \cdot m^{-2}$. Cerebral blood flow was independent of pump flow. At lower pump flow, the percentage of that flow delivered to the brain increased. There was a strong inverse relation between pump flow and cerebral embolization ($r = -0.708$, $P < 0.000$ by Spearman rank order correlation).**

Conclusions: **Cerebral embolization is determined by the CPB flow. At an unchanged mean arterial pressure, as pump flow is reduced, a progressively greater proportion of that flow is delivered to the brain. (Key words: Cerebral blood flow; cerebral emboli; pump flow.)**

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NEUROLOGIC morbidity is a major concern in cardiac surgery. Transcranial Doppler, echocardiographic,[1–3] retinal angiographic,[4,5] pathologic, and radiographic information[6–8] indicate that postcardiac surgical brain injury is in part a function of cerebral embolic events during cardiopulmonary bypass (CPB). Emboli have been detected in 100% of patients undergoing CPB,[4] and the periods of embolic risk during cardiac operations are well-characterized. Most embolization occurs at the time of aortic cannulation, at the onset of CPB, after release of the aortic clamp, and during the early phases of ejection after cross-clamp removal.[2,3,9] After the release of the aortic cross-clamp, as much as 50% of the total amount of Doppler-detected emboli may occur. Additionally, the CPB apparatus is thrombogenic. Even with "adequate" heparinization, thrombin is generated, platelets are activated and aggregated, and these are incompletely trapped by bypass filters.[10–12] This activation of blood elements may also increase cerebral embolic risk.

Although technical interventions, such as the use of membrane oxygenators or arterial line filters,[1,13] and greater surgical attention to embolic risk[14,15] may decrease embolic events, physiologic interventions should also be relevant. We previously demonstrated in swine that manipulation of carbon dioxide during a period of embolic risk can reduce cerebral and ocular embolization by more than 50%.[16] There is indirect evidence to suggest that an increase in CPB pump flow might also reduce cerebral embolization.

Various investigators have demonstrated that cerebral blood flow during CPB is unaffected by pump flow if mean arterial pressure (MAP) is maintained within the autoregulatory range.[17–19] From this, it follows that, as pump flow is reduced, a greater proportion of the bypass flow is delivered to the brain.[17,18,20] Therefore, if a given number of emboli are generated in the aorta, a greater proportion should be delivered to the brain during reduced-bypass flow conditions. The purpose of this study was to determine whether CPB pump flow during a period of embolic risk is a determinant of cerebral embolization.

Methods

After review and approval by the Mayo Clinic and Foundation Institutional Animal Care and Use Committee, 20 unmedicated, fasting, adult, 18- to 22-kg (body surface area [BSA] calculated as 0.12 (body weight in kg)$^{2/3}$) mongrel dogs were studied. The dogs were placed in a Plexiglas box (Rohm & Haas, Philadelphia, PA) and anesthesia was induced with 3 to 4% halothane. Peripheral intravenous access was then secured, muscle relaxation was obtained with pancuronium 0.1 mg/kg, and the trachea was intubated. Ventilation was controlled to maintain arterial carbon dioxide tension (Pa_{CO_2}) at 35–40 mmHg and an arterial oxygen tension (Pa_{O_2}) > 150 mmHg. Anesthesia was maintained with high-dose fentanyl and midazolam (bolus: 250 $\mu g \cdot kg^{-1}$ fentanyl and 350 $\mu g \cdot kg^{-1}$ midazolam, followed by infusion: fentanyl 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and midazolam 9.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In canines, this anesthetic has been shown to prevent movement in response to a surgical stimulus.[21,22] Muscle relaxation was maintained by continuous infusion of pancuronium (0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

A 10-cm 18-gauge catheter was inserted into a femoral artery for MAP measurements and blood sampling. For CPB, a left-sided thoracotomy was performed. Heparin (350 U/kg intravenous) was given for anticoagulation. The bypass machine was primed with 1,000 ml Plasmalyte (Baxter, Deerfield, IL). Venous drainage to the extracorporeal circuit was by a 36-French cannula placed in the right atrium *via* the right atrial appendage. The blood was circulated by a centrifugal pump through a combined heat exchanger–hollow fiber oxygenator (Bentley Spiral Gold, Irvine, CA) and returned *via* a cannula (4.5 mm ID) into the root of the aorta. A 40-μm arterial line filter (Bentley Gold, Irvine, CA) was included in the circuit distal to the oxygenator.

Cardiopulmonary bypass was then undertaken, and nasopharyngeal temperature, measured using a thermocouple, was maintained at 35°C, hemoglobin at 7.5–8.5 $g \cdot dl^{-1}$, Pa_{CO_2} at 35–40 mmHg, using α-stat management, and Pa_{O_2} at 150–250 mmHg. MAP was maintained at 65–75 mmHg by altering bypass pump flow rate. No vasoconstrictors or vasodilators were used. When steady state CPB conditions (as defined previously) were reached, preembolization regional CBF was determined. Within 10 min of CBF measurement, an embolic load was delivered. The embolic load consisted of 1.2×10^5 67 μm orange (540–560 nm) (1 ml) dyed fluorescent polystyrene microspheres (Molecular Probes, Eugene, OR). They were diluted in 9 ml dextran 70, 6%, with 0.025% Tween 80, sonicated and vigorously vortexed, and injected over 5 min into the aortic inflow line distal to the arterial filter. After each injection, the syringe containing the microspheres was flushed with 20 ml dextran 70, 6%, and also injected into the aortic cannula.

Ten minutes before embolization, regional CBF was measured with 15 μm blue-green (430–474 nm) labeled microspheres. At 15 and 45 min after embolization, regional CBF was determined using 15 μm yellow-green (505–515 nm) and 15 μm red (580–605 nm) labeled polystyrene microspheres (Molecular Probes, Eugene, OR), respectively, using the blood reference sample method.[16,23] Four million microspheres (4 ml) were diluted in 6 ml dextran 70, 6%, with 0.025% Tween 80, sonicated, and vortexed, and microspheres were injected over 60 s into the aortic inflow line distal to the arterial line filter. Beginning 30 s before microsphere injection, a reference blood sample was obtained over 4 min. Reference blood was drawn from the femoral artery into a glass syringe by a Harvard withdrawal pump (Harvard Apparatus, Holliston, MA) at 4.9-ml/min. This was transferred into labeled vials; syringes and extension lines were carefully rinsed.

After completion of the experiment, the heart was fibrillated and CPB was discontinued. Animals were killed, the calvarium was opened, and the brain was excised. Tissue samples of the frontal and temporal lobes, the internal capsule, the thalamus, the brain stem, and the cerebellum were obtained. One-gram sections were taken from the respective sites of each hemisphere. Blood and tissue samples were allowed to autolyse in the dark for 10–14 days. Thereafter, microspheres were recovered from tissue by the sedimentation method using previously described techniques.[16,23] The recovery of microspheres from reference blood samples followed a commercially available protocol (Nu-Flow Extraction Protocol 9507.2, Interactive Medical Technology, West Los Angeles, CA). Blood and tissue samples (in 2-ethoxyethyl acetate) both were placed in the dark for 5 days.[16]

The intensity of fluorescence in tissue and blood samples was determined by spectrofluorometers (SLM 8100; SLM-AMINCO, Rochester, NY). The fluorescence of each sample was measured at its specific excitation–emission wavelength. The optimal excitation–emission wavelength of each color was determined before each period of spectrofluorometric analysis. Regional CBF was calculated from the intensity of fluorescence in blood and tissue samples using the following formula:

Table 1. Systemic Physiologic Values of Animals for the Four Study Periods

Study Period	Temp (°C)	MAP (mmHg)	Pump Flow ($l \cdot min^{-1} \cdot m^{-2}$)	Pump Flow (% to brain)	Pa_{CO_2} (mmHg)	Hgb (g/dl)
Preembolization	35.4 ± 0.4	67 ± 2	2.1 ± 0.6	2.6 ± 1.0	36 ± 3	8.3 ± 0.8
Embolization	35.4 ± 0.5	67 ± 4	2.2 ± 0.6		36 ± 2	8.3 ± 0.9
Postembolization (15 min)	35.4 ± 0.3	63 ± 15	2.0 ± 0.7	2.7 ± 1.4	36 ± 3	8.3 ± 0.8
Postembolization (45 min)	35.3 ± 0.4	62 ± 15	2.0 ± 0.6	2.6 ± 0.8	36 ± 3	8.2 ± 0.8

Values are mean ± SD (n = 20). No differences were demonstrated between study periods.

Temp = temperature; MAP = mean arterial pressure; Pa_{CO_2} = arterial carbon dioxide partial pressure; Hgb = hemoglobin (% flow to brain was based on the mean CBF measurements in 12 regions, multiplied by brain weight; table 2).

$$CBF\ (ml \cdot 100g^{-1} \cdot min^{-1}) = (R \cdot I_T)/(I_R \cdot Wt)$$

where R is the rate at which the reference blood sample was withdrawn (4.9 ml · min^{-1}); I_T is the fluorescence intensity of the tissue sample; I_R is the fluorescence intensity of the blood sample; and Wt is the weight of the tissue sample (in grams).

To determine the amount of 67-μm orange fluorescent microspheres per tissue sample, a standard curve with known concentrations of orange microspheres was constructed. The relation between fluorescence intensity and microsphere number is essentially linear in dilute samples.[24] The fluorescence intensity of the tissue sample was then determined, and the standard curve was defined by the following equation:

$$I_T = m \cdot C + b$$

From this equation, the concentration of microspheres was calculated as follows:

$$C = (I_T - b)/m$$

where C is concentration (number of microspheres/ml solvent); I_T is the fluorescence intensity of the tissue sample; b is the y-intercept; and m is the slope.[16]

Statistical Analysis

Systemic physiologic data for preembolization, embolization, and the two postembolization periods were analyzed using a repeated measures analysis of variance. When analysis of variance was significant, the Student-Newman-Keuls test was applied. A paired *t* test was used to test adequacy of microsphere mixing by testing for equal distribution of microspheres to the left and right sides of the brain. All subsequent analyses for regional CBF and embolization were performed using the mean across left and right sides of the brain. The mean number of emboli delivered to circumferential arterial territories (frontal and temporal) and penetrating arterial territories (internal capsule and thalamus) was also determined, as was the ratio of regional blood flow to embolization in each brain region. A paired *t* test was used to compare embolization between these regions. For each brain region, preembolic and postembolic blood flows were compared using the repeated measures analysis of variance and the Student-Newman-Keuls test when indicated. The Spearman rank order correlation was used to test the association between embolization and bypass flow and the percent of that flow delivered to the brain and bypass flow. For the purposes of illustration, the 20 animals were divided into two groups *post hoc,* and the embolization in the 10 animals with the highest pump flows was plotted against the 10 animals with the lowest pump flow at embolization. All data are presented as mean ± SD. A P value < 0.05 was considered significant.

Results

Systemic physiologic data for the four study periods are presented in table 1. Bypass flow, temperature, hemoglobin, MAP, and Pa_{CO_2} did not differ during any of the four study periods.

Regional CBF and embolization values did not differ between left and right brain regions. Paired left and right preembolic, postembolic I (15 min), and postembolic II (45 min) CBF values and emboli counts were well-matched, indicating adequate mixing of microspheres. Therefore, only the mean values for regional blood flows and embolization are presented.

Before embolization, mean CBF over the 12 brain regions was 52 ± 12 ml · 100 g^{-1} · min^{-1} (table 2). There were no differences between the preembolization mean regional brain CBF, and the cerebral blood flows measured at 15 and 45 min postembolization. Predicted differences in blood flow between brain regions, such as

Table 2. Regional Cerebral Blood Flow (ml · 100 g^{-1} · min^{-1}) in Preembolic, Postembolic (15 min) and Post Embolic (45 min) Study Periods

Region	Preembolic	Postembolic (15 min)	Postembolic (45 min)
Frontal	67 ± 21	63 ± 35	59 ± 16
Temporal	61 ± 17	60 ± 28	57 ± 14
Internal capsule	26 ± 4	22 ± 8	21 ± 6
Thalamus	59 ± 13	54 ± 23	51 ± 11
Brain stem	40 ± 19	41 ± 19	44 ± 17
Cerebellum	60 ± 17	60 ± 25	57 ± 14
Mean regional brain	52 ± 12	50 ± 21	48 ± 10

Values are mean ± SD (n = 20). There were no differences demonstrated between the three study periods.

grey and white matter were also shown (frontal and temporal *vs.* internal capsule: $P < 0.000$). Mean CBFs for each region, the sum over all 12 brain regions during the preembolic, and two postembolic periods are presented in table 2. The percentage of the total bypass flow delivered to the brain in the three CBF measurement periods is also provided (table 1). As the total pump flow decreased, a proportionately greater percentage of that flow was delivered to the brain (r = −0.803, $P < 0.000$ for preembolization; r = −0.752, $P < 0.000$ for postembolization[15]; r = −0.698, $P = < 0.000$ for postembolization[45] periods). Figure 1 shows the relation between pump flow and the percent of that flow delivered to the brain in the preembolization period (r = −0.803, $P <$ 0.000).

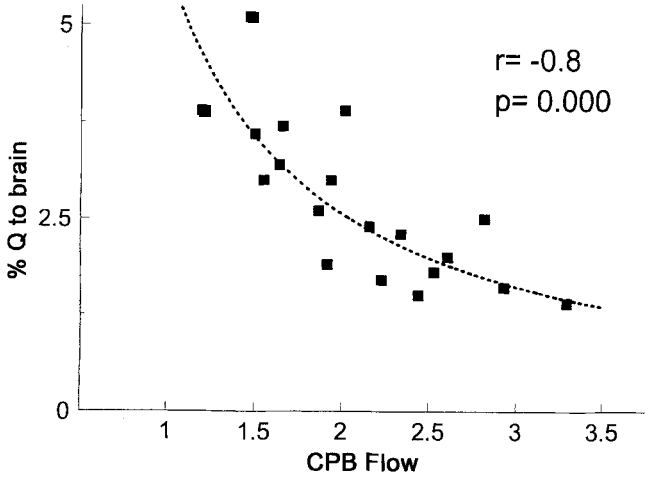

Fig. 1. Relation between pump flow (Q̇) (l · min^{-1} · m^{-2}) and percentage of the total Q̇ delivered to brain for each animal. This figure is generated from 20 individual values in the immediate preembolization period. Two data points are superimposed. (r = −0.803, $P < 0.000$ by Spearman rank order correlation; the regression line is by best-fit).

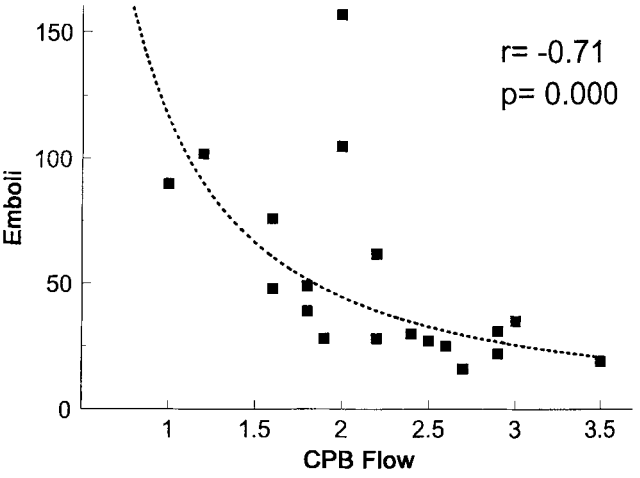

Fig. 2. Relation between pump flow (Q̇) (l · min^{-1} · m^{-2}) and cerebral embolization. A significant correlation (r = −0.708, $P < 0.000$ by Spearman rank order correlation; the regressions line is by best-fit) exists between Q̇ and the mean number of emboli delivered to the brain. All 20 animals (■) are represented. Two data points are superimposed.

At the time of embolization, the MAP in the 20 animals was 67 ± 4 mmHg, and the range of CPB flow resulting in this MAP was 0.9-3.5 l · min^{-1} · m^{-2}. The mean number of emboli over all 12 brain regions was 52 ± 37 microspheres/g. A strong correlation existed between the number of emboli delivered to the brain and the bypass flow (r = −0.708, $P < 0.000$) (fig. 2). For all animals, the mean brain weight in these animals was 83 ± 6 g; therefore, the estimated total count of cerebral emboli was 4,223.

More emboli were found in circumferential arterial territories (frontal, temporal) than in penetrating arterial territories (internal capsule and thalamus). The mean number of emboli/g was 83 ± 65 in circumferential and 28 ± 19 in penetrating arterial territories ($P = < 0.000$). The preembolization CBF was equivalent in frontal, temporal, and thalamic regions (table 2). However, embolization to the thalamus was approximately one half the embolization to the frontal and temporal regions (fig. 3). Similarly, internal capsular blood flow is approximately half that of frontal and temporal regions, whereas embolization to internal capsule is less than one fifth the embolization to frontal and temporal region (table 2 and fig. 3). The regional CBF to emboli ratios were 1.2 ± 0.7 in the circumferential territories (and equivalent in frontal temporal and cerebellar tissues) and 0.6 ± 0.6 in the penetrating arterial territories ($P < 0.000$). This reduction in embolization relative to the regional blood flow suggests trapping of emboli in the circumferential terri-

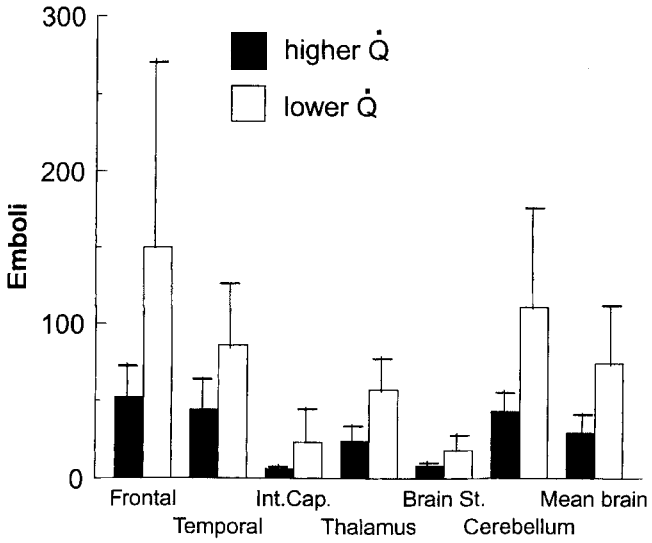

Fig. 3. Regional distribution of cerebral emboli between animals with higher (2.7 ± 0.4) (■) and lower (1.6 ± 0.3 l · min^{-1} · m^{-2}) (□) bypass flow from a *post hoc* analysis. Values are mean ± SD emboli/g (n = 10 in each group).

tories. Embolization to the brain stem and cerebellum were 13 ± 9 and 77 ± 59 emboli/g, respectively.

Embolization did not alter postembolic regional CBF. The mean global postembolic CBFs at 15 and 45 min were 50 ± 21 and 48 ± 10 ml · 100g^{-1} · min^{-1}, respectively, and did not differ from the preembolization CBF (table 2). *Post hoc,* the 20 animals were grouped into those 10 with the highest pump flow at embolization (mean 2.7 ± 0.4 l · min^{-1} · m^{-2}) and those with the lowest pump flow (mean 1.6 ± 0.3 l · min^{-1} · m^{-2}) at embolization. Figure 3 shows the mean embolization in each brain region and the total measured cerebral embolization in these two groups. In the 10 animals with the higher CPB flow, the mean total count of cerebral emboli was 2,450 (2.0% of total delivered to the aortic inflow line). In the 10 animals with the lower CPB flow, the mean total cerebral embolization was 5,993 (or 5.0% of total delivered into the aortic inflow line). The statistical evaluation of the relation between pump flow and embolization was independent of this *post hoc* division.

Discussion

Neurologic injury is a leading cause of morbidity after cardiac surgery. Stroke complicates the procedure in 1–8.9% of cases, and cognitive impairment may occur in more than 50% of patients.[25–27] The cause of this function is multifactorial and probably includes regional cerebral hypoperfusion and embolization.[3,4,28,29] Technical interventions[1,13,15] and greater surgical attention to embolic risk[14] decrease embolic events. Physiologic interventions, such as reducing temperature or Pa_{CO_2} at the time of embolic risk, may also be relevant.[16]

Although counterintuitive initially, an increase in CPB pump flow might also be expected to reduce cerebral embolization. At lower bypass flows, CBF is preserved by shunting of blood flow away from splanchnic organs.[18,20,30] As such, as total pump flow is reduced, a greater proportion of bypass flow is directed to the cerebral circulation (fig. 1). Therefore, if a given number of emboli are generated in the aortic root or left ventricle during CPB, a greater portion should be delivered to the brain when bypass flow is reduced.

The periods of embolic risk during cardiac operations are well-characterized. Transcranial and carotid Doppler and transesophageal echocardiography indicate that most embolization occurs during well-defined periods.[2,3,31] Our findings would suggest that a higher flow during these periods of embolic risk might greatly reduce the amount of emboli delivered to the brain.

Embolization to a given tissue depends on tissue blood flow and embolus size.[16,32] In this study, as in a previous one, we demonstrated the importance of both variables. Tissues with high blood flow (cortical tissues) received more emboli than tissues with lower blood flow (internal capsule). Additionally, the number of emboli distributed to deeper brain structures, supplied by smaller penetrating arteries, (thalamus and internal capsule) is low, relative to their blood flow. This trapping of emboli in the larger circumferential arteries indicates the independent effect of vascular territory on regional embolization.[16,32] In our study, brain stem embolization was low, relative to its blood flow, but the brain stem is not supplied by penetrating arteries. Based on the data provided, we are unable to determine the cause for the low emboli counts in the brain stem of these animals, but it could be related to the vertebrobasilar origin of brain stem flow. Clinically, embolic stroke in the vertebrobasilar system also is less common than in cortical areas despite blood flow, which approximates that of the hemispheres.[33,34]

It might be argued that a polystyrene microsphere is an inadequate model of cerebral embolization. We chose total microsphere number, weight, volume, and size within the range, which may be identified by echocardiography and transcranial Doppler and in histologic or postmortem examination.[1,3,31] The total embolization in this experiment also approximates what may occur dur-

ing clinical CPB.[3] In our 20-kg dogs, 120,000 emboli weighing ≈ 20 mg with a volume of ≈ 19 mm^3 were given systemically; of this, the cerebral embolic load was approximately 4,200 or 0.7 mg. In humans, the total cerebral embolization has been estimated to be as high as 276 mm^3.[3] Thus, even correcting for the smaller size of the dog brain, we are probably delivering a smaller volume and weight of emboli on a per-gram basis than occurs during clinical CPB in many of our patients. The density and spherical nature of these beads are not similar to the emboli generated during CPB, but the microspheres model is the only reliable one for this type of work. Bead size is extremely standard, and known quantities of beads can be delivered. Finally, the use of latex microspheres is an established model of regional ischemia.[35,36]

It is also important to note that animals did not show significant decreases in postembolic CBF measurements. This shows that the embolic load used in this study was not overwhelming and that global CBF may be maintained after moderate embolization. However, this result would not be expected with a greater total embolization or obstruction of major arteries or arterioles by large atheroembolic plaque.

A criticism might also be raised that increasing pump flow rate might generate more emboli by a "sandblasting" effect and, thus, increase total cerebral embolization. Although this idea often is discussed and cannulae have been designed to diffuse the stream of blood flow exiting the aortic cannula, we are not aware of literature that supports this idea. That hypothesis also is difficult to test in a controlled fashion. Nonetheless, we would agree that our study does not address this question. However, the periods of embolic risk are well-characterized. These periods are largely surgical-event specific and do not appear to be related to sandblasting by the arterial inflow.

Finally, our investigation determined the effect of CPB flow on embolization when different animals were exposed to an embolic load at differing flows. We did not determine cerebral embolization during two different flow conditions in the same animals. We avoided that design because we expected that the first embolization would alter the second embolization. As such, there is an experimental gap (although not a logical one) to the proposition that an increase in CPB flow during periods of embolic risk would reduce delivery of emboli to the brain. Given the relation we describe between pump flow and the percent of that flow delivered to the brain, higher CPB flows will shunt emboli to noncerebral organ beds and reduce the concentration of emboli per volume of blood delivered to the brain.

In summary, our study clearly showed that pump flow is an important determinant of cerebral embolization. A high pump flow rate decreases the distribution of emboli to the cerebral circulation when a fixed embolic load enters the aorta, whereas a lower pump flow rate increases it. Increasing pump flow during periods of embolic risk may reduce cerebral embolization. Similar to decreasing Pa_{CO_2},[16] this intervention is simple, rapidly reversible, and virtually without cost. These observations have potentially important implications for clinical CPB practice.

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