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Toward Understanding Cerebral Blood Flow during Cardiopulmonary Bypass

Implications for the Central Nervous System

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This research¹ began in the early 1980s when cardiac surgery was growing rapidly because of the relatively recent acceptance of coronary artery bypass grafting as an effective



J. G. Reves, M.D., at the Charleston Battery, circa 1984.

Factors and Their Influence on Regional Cerebral Blood Flow during Nonpulsatile Cardiopulmonary Bypass. By Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, and Freeman AM. *Ann Thorac Surg.* 1984; 38:609–13. Reprinted with permission.

Abstract: In this study, we examined the relationship of regional cerebral blood flow (CBF) to mean arterial pressure, systemic blood flow, partial pressure of arterial carbon dioxide (PaCO₂), nasopharyngeal temperature, and hemoglobin during hypothermic nonpulsatile cardiopulmonary bypass (CPB). Regional CBF was determined by clearance of xenon 133 in 67 patients undergoing coronary bypass grafting procedures. There was a significant decrease in regional CBF (55% decrease) during CPB, with nasopharyngeal temperature and PaCO₂ being the only two significant factors ($p < 0.05$). In a subgroup of 10 patients, variation of pump flow between 1.0 and 2.0 L/min/m₂ did not significantly affect regional CBF. We conclude that cerebral autoregulation is retained during hypothermic CPB. Under the usual conditions of CPB, variations in flow and pressure are not associated with important physiologic or detrimental clinical effects.

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treatment for ischemic heart disease. The anesthesiology subspecialty of cardiac anesthesia was in its formative period,^{2,3} and there were many questions being raised about outcome and more importantly what factors under the control of anesthesiologists might impact outcome. One question that Arthur Keats, M.D., raised in his iconoclastic Rovenstine Lecture of 1983⁴ (after we had already completed our study) was the relevance of pump flow (systemic blood flow) and blood pressure during cardiopulmonary bypass (CPB) to outcome.

Anesthesiologists, perfusionists, and surgeons tended to have strong opinions on what the controllable variables should be during CPB. These opinions were based not on experimental evidence, but rather for the most part on institutional preference, historical evolution, or some seemingly divine guidance. Thus, after consulting with neurosurgical anesthesia colleagues Philippa Newfield, M.D., of University of California San Francisco in San Francisco, California; Robert McKay, M.D., of the University of Alabama Birmingham in Birmingham, Alabama; and John Michenfelder, M.D., of the Mayo Medical School in Rochester, Minnesota, we undertook the study titled “Factors and Their Influence on Regional Cerebral Blood Flow during Nonpulsatile Cardiopulmonary Bypass.”¹ This was an observational study of 67 patients designed to answer the question: What controllable factors influence regional cerebral blood flow during the extremely abnormal conditions of CPB? We hoped this might provide evidence to guide our practice.

At the time ¹³³Xe clearance (see fig. 1) was routinely used to monitor regional (hemispheric) cerebral blood flow at the

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Fig. 1. Apparatus for measuring cerebral blood flow in a patient undergoing coronary artery bypass grafting at Duke University, Durham, North Carolina. There are bilateral detectors of ^{133}Xe and a jugular bulb catheter for sampling of jugular blood used to compute cerebral metabolism. This technique was routinely used in the many studies at Duke, but a simpler single detector and no jugular bulb catheter were used in the classic paper.¹

Mayo Clinic (Rochester, Minnesota) during carotid endarterectomy surgery, and we believed it would be useful to determine the influence of temperature, pump flow, blood pressure, hematocrit, and Paco_2 on cerebral blood flow. This study was done at the University of Alabama Birmingham under the leadership of John Kirklin, M.D., the pioneering cardiac surgeon from the Mayo Clinic who first successfully used the Gibbon oxygenator in a series of patients.⁵ Cardiac surgery was arguably as advanced in Birmingham as any place in the country at that time. Kirklin had recruited anesthesiologists William A. Lell, M.D., as chief and Paul N. Samuelson, M.D., and this author to establish cardiac anesthesiology in Birmingham.

One goal of this interdisciplinary team approach was to establish practice on a firm scientific foundation. The fact that ^{133}Xe cerebral blood flow measurements were used at the Mayo Clinic made it relatively easy for our surgical colleagues to agree to the methodology for the research. The motivation for the work was that there were decisions about flow, temperature, hematocrit, Paco_2 , and especially blood pressure being made every day in a climate of ignorance and uncertainty. These are not the best conditions for patient care.

Our findings revealed that cerebral blood flow was significantly reduced with hypothermia (see fig. 2).

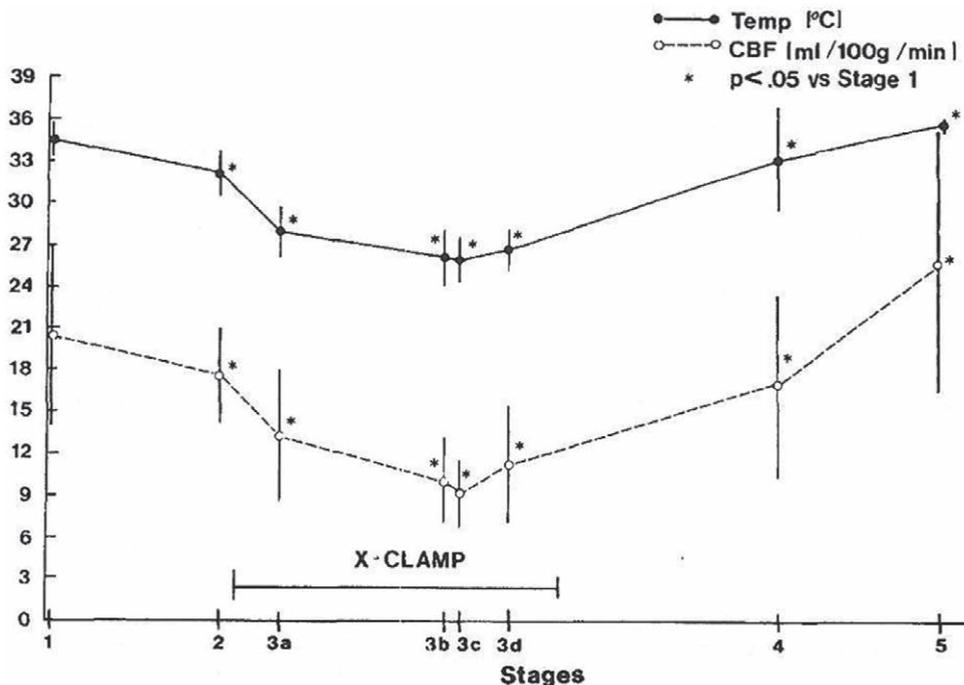


Fig. 2. Cerebral blood flow (CBF) and nasopharyngeal temperature (Temp) during stages of the coronary artery bypass surgery. Note the parallel changes in temperature and CBF. Stage 1 = 5 to 10 min before cardiopulmonary bypass (CPB); Stage 2 = 5 to 10 min after initiation of CPB; Stage 3a = first injection of ^{133}Xe during CPB with aorta cross-clamped (X-CLAMP); Stage 3b = second injection during X-CLAMP; Stage 3d = fourth injection during X-CLAMP; Stage 4 = during CPB after release of aortic cross-clamp; and Stage 5 = after completion of CPB. Data are shown as mean \pm SD. Reprinted with permission from Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, Freeman AM: Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1984; 38:592–600. Copyright © 1984 Elsevier.

Furthermore, we found that PaCO_2 had a significant impact on regional cerebral blood flow, but that blood pressure and pump flow had minimal impact on cerebral blood flow. The pump flow data were generated by randomly measuring cerebral blood flow at various pump flows (see fig. 3) to answer the crucial question of how important pump flow was to cerebral blood flow. Our results led us to conclude that the most important variables influencing cerebral blood flow were temperature and PaCO_2 . Furthermore, to explain the tight tracking of cerebral blood flow with temperature we postulated that cerebral metabolism was coupled with cerebral blood flow during CPB, meaning that as temperature (and the metabolism of the brain) decreased there was a parallel decrease in cerebral blood flow. In a later study at Duke University (Durham, North Carolina) using alpha-stat management,⁶ we showed the intact coupling of temperature and cerebral metabolic rate of oxygen (see fig. 4.)

In the original study,¹ we also observed that cerebral blood flow remained relatively constant over a wide range (30 mm Hg to 100 mm Hg) of mean systemic arterial blood pressures. This led us to conclude that with constant temperature, pump flow, hematocrit, and PaCO_2 autoregulation remained intact. We later validated our cerebral blood flow

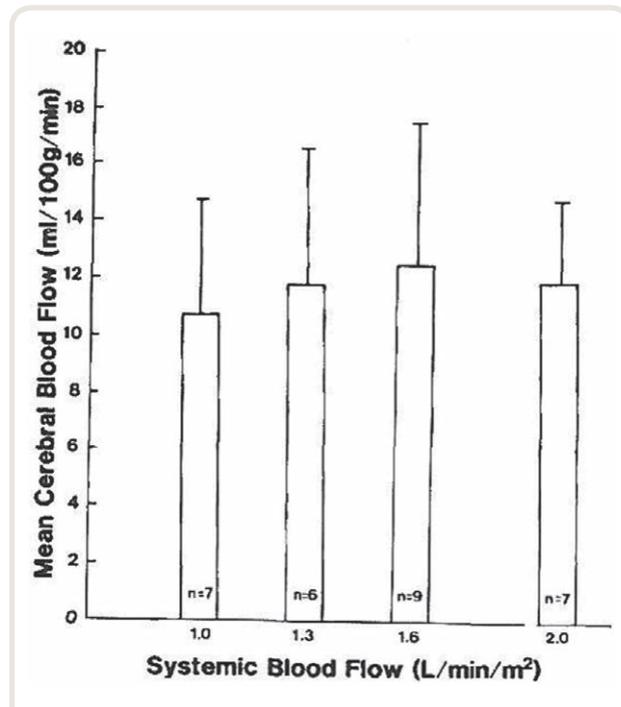


Fig. 3. Cerebral blood flow at various systemic blood flows in 10 patients during cardiopulmonary bypass. The four randomized flows are 1.0, 1.3, 1.6, and 2.0 l/min/m² and all at the same temperature, PaCO_2 , and perfusion pressure. Reprinted with permission from Govier AV, Reves JG, McKay RD, Karp RB, Zorn GL, Morawetz RB, Smith LR, Adams M, Freeman AM: Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1984; 38:592–600. Copyright © 1984 Elsevier.

measurement method during CPB at Duke University using a canine model comparing ¹³³Xe clearance with the Kety-Schmidt technique.⁷

Unknown to us, contemporaneously, in Copenhagen, Denmark, Leif Henriksen, M.D., of the Department of Neurology, Rigshospitalet, and colleagues had embarked on a study similar in design to ours in 29 patients.⁸ They also were exploring the effect of CPB on cerebral blood flow, and they published their work the year our abstract came out.⁹ Parts of the Copenhagen study group results were at variance with ours, and their conclusions were astonishingly different. They concluded that during CPB “there was impairment of autoregulation.” Their findings did show a significant decrease in cerebral blood flow with temperature and a direct relationship with PaCO_2 , but they also found a direct relationship between perfusion pressure (systemic blood pressure) and cerebral blood flow. Thus, they concluded that there was a loss of autoregulation. The differing conclusions, both published in alternate cardiac “surgical” journals, led to greater confusion and uncertainty than before either paper was published regarding cerebral blood flow and blood pressure. This, of course, is an example of just how frustrating or messy clinical research can be to those who want simple answers to simple questions.

John Murkin, M.D., of the University of Western Ontario, London, Ontario, Canada, came to the rescue in

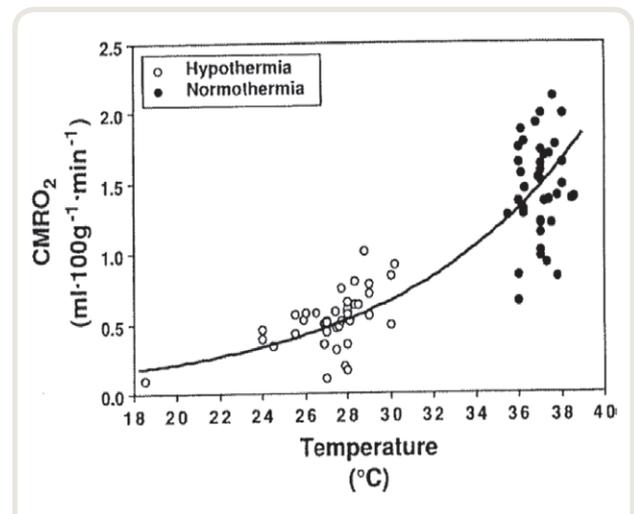


Fig. 4. Cerebral metabolic rate of oxygen (CMRO_2) expressed in relation to temperature based on the equation $\ln(\text{CMRO}_2) = a + b \cdot T$ where \ln is the natural logarithm function, T is the temperature in degrees centigrade, a is the intercept, and b is the slope. Based on data from 41 patients undergoing coronary artery bypass graft surgery at constant pump flows of 2 l/min/m² using alpha-stat blood gas measurement and keeping the PaCO_2 at 35 to 40 mm Hg and blood pressure 50 to 80 mm Hg. Reprinted with permission from Croughwell N, Smith LR, Quill T, Newman M, Greeley W, Kern F, Lu J, Reves JG: The effect of temperature on cerebral metabolism and blood flow in adults during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1992; 103:549–54. Copyright © 1992 Elsevier.

1987 with what can best be termed investigative reporting by explaining clearly why these two early reports had seemingly conflicting results.¹⁰ Cerebral blood flow is responsive to PaCO_2 , and the crucial difference between the practice at each institution was correcting arterial blood gases for temperature or not. In Copenhagen, temperature correction was used. This pH-Stat method leads to addition of carbon dioxide, producing a relative respiratory acidosis that causes near maximal dilation of the cerebrovasculature. On the other hand, in Birmingham, blood gases were not corrected for temperature (alpha-stat method). Thus, the absolute carbon dioxide concentrations were lower, which enabled the cerebrovasculature to constrict or dilate in response to other regulatory factors such as metabolism. In other words, alpha-stat management does not maximally dilate cerebral arterioles.

Thus, with alpha-stat blood gas management cerebral autoregulation remains intact during CPB, but with pH-stat blood gas management cerebral blood flow is flow and pressure dependent because vessels are maximally dilated by the added carbon dioxide. Murkin *et al.*¹⁰ concluded that pH-stat blood gas management “uncouples cerebral flow/metabolism and probably impairs cerebral autoregulation.” We learned that it is important to be clear on the method of blood gas management when attempting to define factors that affect cerebral blood flow. In subsequent studies, we always offered the caveat that our observations were made using alpha-stat management.

Our paper also addressed the new question regarding non-stroke central nervous system outcome after CPB as measured by neurocognitive testing.^{1,11} What is now called “neurocognitive dysfunction” had been reported by Slogoff *et al.*¹² in Houston, Texas, in 1982 and Breuer *et al.*¹³ in Cleveland, Ohio, in 1983. We attempted to relate changes in the Mini-Mental-State Examination with the observed changes in cerebral blood flow and found no correlation.¹¹ However, this negative study with an admittedly imprecise test of cognition led to a very productive line of investigation by the Duke University Neurologic Outcome Research Group headed by Mark Newman, M.D. Using much more sensitive and specific measures of cognition,¹⁴ Newman went on to show that the cognitive dysfunction immediately after cardiac surgery was a risk for a return of dysfunction 5 yr later¹⁵ and associated with some loss in quality of life indicators.¹⁶ In fact, an entire field of investigation has evolved from these early findings on nonstroke central nervous system changes in cardiac as well as noncardiac surgical procedures, particularly in the elderly.¹⁷

In reflecting on the past 35 yr in this field, it is clear that we can base modern CPB management on a large number of studies that have provided evidence for clinical decision-making during CPB.^{18–21} However, the causes of neurocognitive dysfunction after CPB and more importantly the role of cerebroprotective strategies during CPB remain to be elucidated.^{21,22} Nevertheless, it has been gratifying to see some light shed on the darkness that still threatens. As Churchill observed in an entirely different context:

“Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”²³

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Competing Interests

Dr. Reves is scientific director of SimTunes LLC, Charleston, South Carolina, and declares no competing interest.

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