

Pa_{CO₂} Management during Cardiopulmonary Bypass: Intriguing Physiologic Rationale, Convincing Clinical Data, Evolving Hypothesis?

IN THIS ISSUE, Bashein *et al.* establish a milestone in the longstanding debate about the preferable level of Pa_{CO₂} and pH during cardiopulmonary bypass (CPB).¹ Their well-designed, carefully analyzed study suggests that Pa_{CO₂} management during CPB does not influence postoperative neuropsychologic outcome.¹ An appreciation of this important work requires examination of four issues: 1) the controversy regarding Pa_{CO₂} management during CPB; 2) the frequency of neurologic dysfunction following cardiac surgery; 3) the quantification of neurologic and neuropsychologic injury; and 4) the potential relationship of Pa_{CO₂} management during hypothermic CPB to neurologic outcome.

The Controversy

Physiologists and clinicians have attempted for decades to define normal levels of Pa_{CO₂} and pH under hypothermic conditions. One option, termed α -stat management, maintains Pa_{CO₂} and pH at 40 mmHg and 7.40, respectively, as measured in the blood gas analyzer at 37°C. The alternative, pH-stat strategy maintains Pa_{CO₂} and pH at 40 mmHg and 7.50, after correction for body temperature. At a body temperature of 28.5°C, the pH-stat approach increases Pa_{CO₂} by 50% (table 1).

The physicochemical argument for α -stat management is that the isoelectric point of water, the pH at which water maintains a constant ratio of OH⁻ to H⁺ ions, increases as temperature decreases.² A physiologic, but species-dependent, argument is that spontaneously cooling poikilothermic animals (*e.g.*, reptiles and amphibians) appear to follow an α -stat pattern.²⁻⁶ In contrast, heterothermic, hibernating mammals undergo changes in pH and Pa_{CO₂} that resemble the pH-stat approach during cooling.²

FREQUENCY OF POST-CPB NEUROLOGIC AND NEUROPSYCHOLOGIC DYSFUNCTION

Detailed neurologic examination discloses early postoperative deficits in 61% of patients following coronary artery surgery, although many of those deficits do not grossly impair long-term function.⁷ In an even higher percentage of patients, psychomotor performance deteriorates between preoperative and postoperative testing.⁷⁻⁹ Deterioration of neuropsychologic performance is most likely in patients who also develop neurologic deficits,^{10,11} suggesting a common etiology for the two types of abnormalities.

Both neurologic and neuropsychologic deficits appear to be linked to perioperative ischemic injury. Åberg *et al.* measured increased cerebrospinal fluid levels of adenylate kinase, an enzymatic marker of ischemic neural damage, in more than 50% of patients following valvular or coronary surgery.¹² The authors positively correlated neuropsychologic deterioration with increases in adenylate kinase.¹² Although the economic consequences of subtle neurologic and neuropsychologic injury have not been quantitated, clinically evident neurologic events increase the duration of hospital stay threefold following myocardial revascularization.¹³

QUANTIFICATION OF NEUROLOGIC AND NEUROPSYCHOLOGIC INJURY

Quantification of neurologic and neuropsychologic complications requires rigorous preoperative and postoperative evaluation. Most lesions that are detected with prospective testing would not otherwise be recorded in the medical record.¹⁰ Neuropsychologic testing, though unfamiliar to many clinicians, is highly quantitative. Such tests have clearly demonstrated deterioration in psychomotor performance as a result of chronic disease and have been correlated with impaired quality of life.

Grant *et al.* evaluated 303 chronically hypoxic patients who participated in two major clinical trials, the Nocturnal Oxygen Therapy Trial (NOTT) and the Intermittent Positive Pressure Breathing (IPPB) trial, and identified a strong correlation between the severity of hypoxemia and

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TABLE 1. α -Stat and p H-Stat Levels of P_{aCO_2} at 28.5° C

| | p H-Stat | α -Stat |
|--|------------|----------------|
| P_{aCO_2} (at 28.5° C body temperature) | 40 mmHg | 27 mmHg |
| P_{aCO_2} (at 37° C, blood gas analyzer) | 60 mmHg | 40 mmHg |

decrements in psychomotor performance.¹⁴ More importantly, they demonstrated that neuropsychologic dysfunction associated with chronic hypoxemia correlates with deterioration in quality of life.¹⁵ In those two series, the duration of the test battery exceeded the practical limits that a postoperative surgical patient will tolerate without excessive fatigue; however, several essential components of the battery resemble those used by Bashein *et al.*¹ Table 2 summarizes the results of two tests, Trail Making B and the Tapping Test, common to both groups of investigators. Comparison of these results suggests that cardiac surgery produces an acute decrement in psychomotor performance similar in magnitude to that associated with chronic hypoxemia.

However, the circumstances of the testing are dissimilar. Traditionally, extensive batteries of psychomotor tests have been used to compare the performance of groups of individuals, as in the NOTT and the IPPB trial.¹⁴ In such an analysis, baseline data are unavailable; therefore, mean levels of impairment must be correlated with coexisting physiologic or neurologic abnormalities. In contrast, cardiac surgical patients can be examined both pre- and postoperatively. However, comparison of preoperative and postoperative performance is potentially confounded by several variables, including pain, fatigue, analgesic drugs, and practice effects. In the few postoperative days preceding comprehensive evaluation, a brief daily examination will identify the occasional deficit that develops after, rather than during, surgery.

How, then, can an investigator confidently define a postoperative deficit? Some investigators prefer to compare alternative management strategies on the basis of

unequivocal neurologic abnormalities,¹⁶ although such an approach requires a large percentage change in a large number of patients in order to achieve statistical power. Others, such as Bashein *et al.*, have preferred the greater statistical power conferred by a concise, focused neuropsychologic battery, administered after sufficient convalescence (usually about 5–8 days postoperatively) to minimize the effects of pain, fatigue, and drugs.^{1,7,8} Implicit in the decision to compare neuropsychologic outcome is the assumption that neurologic and neuropsychologic outcome should be altered similarly by a given therapeutic intervention. Although few data are available to examine that assumption, it is worth noting that Nussmeier *et al.* demonstrated that thiopental administration during valvular heart surgery significantly reduced major neurologic deficits but did not alter the incidence of deterioration in the performance in Trail Making B.¹⁶

Statistical analysis of changes in neuropsychologic status represents an additional challenge. Bashein *et al.* compared mean group performance in the α -stat and p H-stat groups and found no difference in postoperative outcome.¹ However, assessment of group means may be misleading if some individuals improve because of practice effects while others deteriorate. Therefore, Shaw *et al.* and Harrison *et al.* have defined the number of individual postoperative patients who deteriorate as those whose postoperative score in individual components of the battery has declined more than one standard deviation from the preoperative group mean score. For comparison, in most of the tests used in the NOTT and IPPB Trials, moderately hypoxemic patients performed approximately one-half standard deviation below the mean group performance of age- and education-matched control subjects.¹⁴ The conclusions reached by studies that examine group performance may be radically different than studies that focus on the incidence of individual deterioration. Klonoff *et al.* reported that overall group performance was improved 1 yr following cardiac surgery.¹⁷ In contrast, Venn *et al.* reported that 35% of individual patients showed deficits at a similar postoperative interval.¹⁸

TABLE 2. Comparison of Neuropsychologic Scores

| Test | Chronically Hypoxemic Patients (NOTT and IPPB Trials) | | Cardiac Surgical Patients (Bashein <i>et al.</i>) | |
|--|--|-------------------------|---|--|
| | Control | Moderately Hypoxemic | Preoperative | Postoperative |
| Trail Making B (time in s) | 122 ± 62 | 156 ± 78 | 95.0 ± 38.4 | 134.2 ± 79.1 (α) 144.9 ± 80.2 (p H) |
| Tapping Test (taps per 10 s, dominant hand) | 46.7 ± 8.1 | 42.1 ± 9.8 | 45.0 ± 7.8 | 41.0 ± 14.0 (α) 43.0 ± 13.5 (p H) |

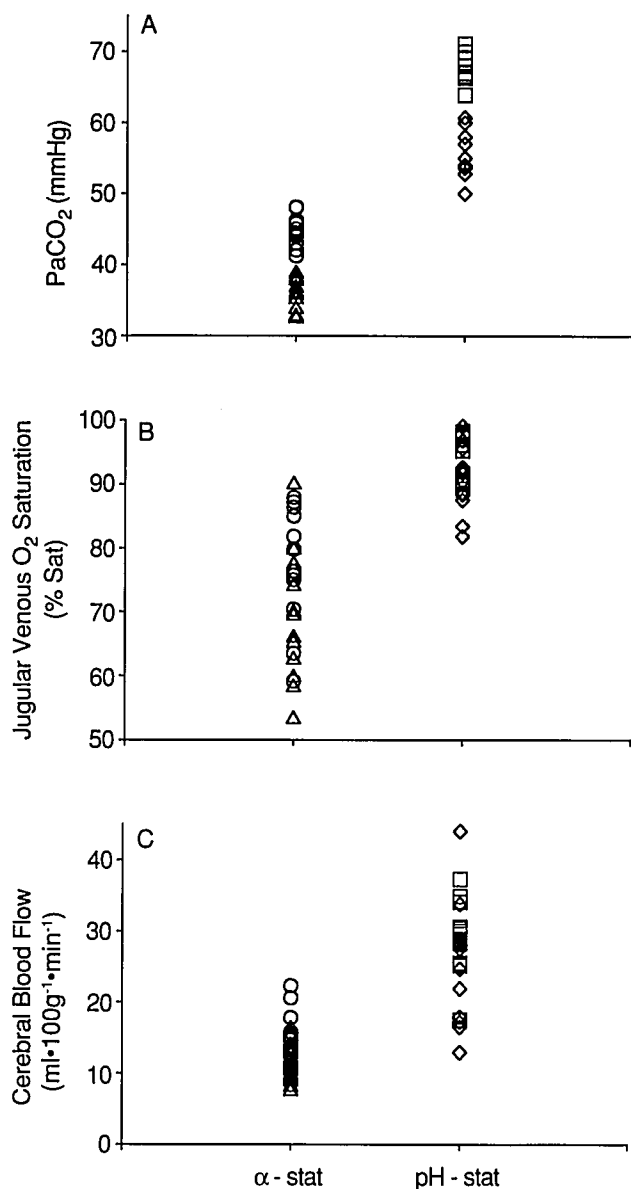


FIG. 1. A displays two levels of PaCO₂, uncorrected for body temperature, measured in 25 patients undergoing cardiopulmonary bypass at a mean temperature of 27.5°C. Patients, randomized to α -stat (open circles and triangles) or pH-stat (open squares and diamonds) management, underwent two measurements of jugular venous bulb oxygen saturation (S_{jv}O₂) and two estimates of cerebral blood flow (CBF), obtained from analysis of the clearance of ¹³³Xenon, at two randomly ordered levels of PaCO₂. Circles represent the higher level of PaCO₂ and triangles the lower level in the α -stat group; squares represent the higher level and diamonds the lower level in the pH-stat group. By experimental design, there is no overlap of PaCO₂ values between the α -stat and pH-stat patients. B demonstrates the considerable overlap of S_{jv}O₂ values in the two groups, although the lowest values are in the α -stat group. C demonstrates that the values for cerebral blood flow also overlap, although the highest values are in the pH-stat group. Therefore, by knowing PaCO₂, one cannot predict individual levels of cerebral blood flow or individual levels of cerebral oxygen extraction.

WHY SHOULD PaCO₂ MANAGEMENT DURING CPB AFFECT NEUROLOGIC OUTCOME?

From a physiologic perspective, the results reported by Bashein *et al.* suggest the impending demise of an intriguing physiologic question. However, any comparison between α -stat and pH-stat management must be based upon presumed differences in the physiologic effects of the two strategies. The two do produce somewhat different average effects on cerebral blood flow (CBF) and metabolism during hypothermic, nonpulsatile CPB. Investigators have demonstrated that the pH-stat approach produces luxury perfusion,¹⁹ impairs autoregulation,²⁰ and uncouples CBF and metabolism.¹⁹ In addition, because the increased PaCO₂ produced by the pH-stat approach increases CBF,²¹ it theoretically could result in the distribution of an increased proportion of embolic debris to the brain rather than the systemic circulation.²² In contrast, the lower CBF associated with the α -stat approach might cause critical hypoperfusion in selected patients. Available data do not quantitate either hypothetical concern, *i.e.*, the risk of increasing cerebral emboli or the risk of cerebral hypoperfusion. Both potential hazards are related to the level of CBF or the level of cerebral metabolism, of which measurement of PaCO₂ is at best an indirect indicator.

To illustrate, figure 1 displays individual data derived from a study of CBF and jugular venous bulb oxygen saturation (S_{jv}O₂) in 25 hypothermic patients ($\approx 27.5^\circ\text{C}$) randomized either to a range of PaCO₂ comparable to α -stat values ($n = 13$), or a range similar to pH-stat values ($n = 12$).²³ As is evident in figure 1A, PaCO₂ in the two patient groups is distinctly different. As figure 1B shows, PaCO₂ fails to predict cerebral oxygen extraction in individual patients. Although S_{jv}O₂, an index of the ability of global CBF to supply cerebral metabolic needs, is generally lower in the α -stat patients, only one-third of patients in the α -stat group have S_{jv}O₂ values lower than those in awake, normothermic patients (fig. 1B). That one-third of patients presumably would include an even smaller number who are at risk for cerebral hypoperfusion. Figure 1C displays CBF values in the same group of patients. Although the patients with the highest levels of flow and therefore the highest theoretical risk for embolic events are in the pH-stat group, CBF clearly exceeds that in the α -stat group in only about one-half of the patients. CBF is determined in part by PaCO₂, as it is by cerebral perfusion pressure, but the choice of a target PaCO₂ during CPB provides limited information about cerebral perfusion.

Accordingly, we conclude that the study by Bashein *et al.* though a major milestone in a protracted, unresolved debate, does not dismiss the question about a preferable level of PaCO₂ during cardiopulmonary bypass. The res-

olution of that question awaits correlation of carefully defined neurologic and neuropsychologic endpoints with measured cerebral circulatory and metabolic changes during CPB.

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References

- Bashein G, Townes BD, Nessly ML, Bledsoe SW, Hornbein TF, Davis KB, Goldstein DE, Coppel DB. A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. *ANESTHESIOLOGY* 72:7-15, 1990
- Reeves RB. Role of body temperature in determining the acid-base state in vertebrates. *Fed Proc* 28:1204-1208, 1969
- Rahn H, Reeves RB, Howell BJ. Hydrogen ion regulation, temperature, and evolution. *Am Rev Respir Dis* 112:165-172, 1975
- Williams JJ, Marshall BE. A fresh look at an old question [editorial]. *ANESTHESIOLOGY* 56:1-2, 1982
- Swain JA. Hypothermia and blood pH. A review. *Arch Intern Med* 148:1643-1646, 1988
- Ream AK, Reitz BA, Silverberg G. Temperature correction of P_{aCO_2} and pH in estimating acid-base status: An example of the Emperor's new clothes? *ANESTHESIOLOGY* 56:41-44, 1982
- Shaw PJ, Bates D, Cartledge NE, French JM, Heaviside D, Julian DG, Shaw DA. Neurologic and neuropsychological morbidity following major surgery: Comparison of coronary artery bypass and peripheral vascular surgery. *Stroke* 18:700-707, 1987
- Harrison MJ, Schneidau A, Ho R, Smith PL, Newman S, Treasure T. Cerebrovascular disease and functional outcome after coronary artery bypass surgery. *Stroke* 20:235-237, 1989
- Smith PL, Treasure T, Newman SP, Joseph P, Ell PJ, Schneidau A, Harrison MJ. Cerebral consequences of cardiopulmonary bypass. *Lancet* 1:823-825, 1986.
- Sotaniemi KA. Cerebral outcome after extracorporeal circulation. Comparison between prospective and retrospective evaluations. *Arch Neurol* 40:75-77, 1983
- Slogoff S, Girgis KZ, Keats AS. Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. *Anesth Analg* 61:903-911, 1982
- Åberg T, Ronquist G, Tyden H, Brunnkvist S, Hultman J, Bergstrom K, Lilja A. Adverse effects on the brain in cardiac operations as assessed by biochemical, psychometric, and radiologic methods. *J Thorac Cardiovasc Surg* 87:99-105, 1984
- Weintraub WS, Jones EL, Craver J, Guyton R, Cohen C. Determinants of prolonged length of hospital stay after coronary bypass surgery. *Circulation* 80:276-284, 1989
- Grant I, Prigatano GP, Heaton RK, McSweeney AJ, Wright EC, Adams KM. Progressive neuropsychologic impairment and hypoxemia. Relationship in chronic obstructive pulmonary disease. *Arch Gen Psychiatry* 44:999-1006, 1987
- McSweeney AJ, Grant I, Heaton RK, Prigatano GP, Adams KM. Relationship of neuropsychological status to everyday functioning in healthy and chronically ill persons. *J Clin Exp Neuropsychology* 7:281-291, 1985
- Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. *ANESTHESIOLOGY* 64:165-170, 1986
- Klonoff H, Clark C, Kavanagh-Gray D, Mizgala H, Muno I. Two-year follow-up study of coronary bypass surgery. Psychologic status, employment status, and quality of life. *J Thorac Cardiovasc Surg* 97:78-85, 1989
- Venn G, Klinger L, Smith P, Harrison M, Newman SP, Treasure T. Neuropsychologic sequelae of bypass twelve months after coronary artery surgery [abstract]. *Br Heart J* 57:565, 1987
- Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: The influence of P_{aCO_2} . *Anesth Analg* 66:825-832, 1987
- Rogers AT, Stump DA, Gravlee GP, Prough DS, Angert KC, Wallenhaupt SL, Roy RC, Phipps J. Response of cerebral blood flow to phenylephrine infusion during hypothermic cardiopulmonary bypass: Influence of P_{aCO_2} management. *ANESTHESIOLOGY* 69:547-551, 1988
- Prough DS, Stump DA, Roy RC, Gravlee GP, Williams T, Mills S, Hinshelwood L, Howard G. Response of cerebral blood flow to changes in carbon dioxide tension during hypothermic cardiopulmonary bypass. *ANESTHESIOLOGY* 64:576-581, 1986
- Murkin JM. Cerebral hyperperfusion during cardiopulmonary bypass: The influence of P_{aCO_2} , Brain Injury and Protection During Heart Surgery. Edited by Hilberman H. Boston, Martinus Nijhoff, 1988, pp 47-66
- Prough DS, Rogers AT, Stump DA, Mills SA, Cordell AR, Gravlee GP, Phipps J, Charles D. Hypercarbia depresses cerebral oxygen consumption during cardiopulmonary bypass. *Stroke* (in press)