CONCLUSION

The results of the review showed no significant difference in fluid balance and urine out put with the addition of mannitol. There was a trend for increased urine output in patients with prolonged bypass time. A prospective randomized control trial with larger patient group and addition of mannitol either in the prime or at a discrete time during bypass to reduce the variability between the groups is recommended.

What Blood Pressure is Appropriate for Cardiopulmonary Bypass and How To Get It

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In 1995, Gold et al. published the results of a randomized clinical trial of elective coronary artery bypass grafting in 248 patients randomized to two groups (1). In one group, mean arterial pressure was maintained between 50 and 60 mmHg during cardiopulmonary bypass and in the other it was maintained between 80 and 100 mmHg. The incidence of combined cardiac and neurological complications was significantly lower in the high pressure group (4.8%) than in the low pressure group (12.9%: $p = 0.026$). Six months postoperatively, the mortality rates were 1.6% and 4%, stroke rates 2.4% and 7.2%, and cardiac complication rates 2.4% and 4.8%. Cognitive and functional status outcomes did not differ between the groups. This study precipitated a change in practice in our unit, more in response to casual discussion than in any formalised way. The use of vasoconstrictors to maintain higher mean arterial pressures has become the norm.

Gold's study was cirticised when published on a number of grounds, notably the unjustifiable technique of selectively pooling data to achieve statistical significance. Other criticisms included the lack of data on the prevalence of post bypass and postoperative hypotension or hypertension.

WHAT IS THE TRUTH OF THE MATTER?

The primary reason for worrying about blood pressure on CPB is the potential for injury to the brain. Adverse cerebral outcomes after cardiac surgery are associated with higher in-hospital mortality, longer hospitalisation, and a higher rate of discharge to other facilities for further care (2). Factors which have the potential to affect neurocognitive outcomes after cardiac surgery include:

1. hypoperfusion (3,4,5)
2. cerebral embolic load (6)
3. hypoglycaemia (6)
4. hypertension (7)
5. atheromatous disease (8)
6. therapeutic agents (9)
7. temperature (10)

Studies of pressure during CPB need to take each of these into account. This has not always been the case. Stockard established the concept of tm^{50} (the integral of perfusion pressure $\leq$50 mmHg over time) (11). We have the opportunity to study this in our own patients.

Cerebral perfusion pressure is the difference between mean arterial pressure and central venous pressure. The argument around perfusion pressure and cerebral blood flow is complicated. Low flow may be associated with hypoperfusion. High flow may increase embolic load. Brown has demonstrated a relationship between embolic load and bypass time (12) which links to other work showing poorer neurological outcomes with increased bypass times. Schmidt has demonstrated that cardiopulmonary bypass is associated with a significantly higher rate of cerebral injury in patients who were hypertensive preoperatively (7). Technical matters are also important (13)—including the design of equipment used during CPB (14,15). Putting the patient head down at critical moments in the procedure may reduce embolisation to the brain (16). Reducing the haematocrit may improve flow but the lowest haematocrit during CPB is an independent risk factor for mortality (risk is increased if the haematocrit $\leq$ 14%) (17). Transient hypertension during cardiac surgery has been associated with stroke. High perfusion pressure may be associated with more damage to blood elements and thereby exacerbate the inflammatory response to CPB. It may also compromise the surgical field.

Table 1. Some factors which affect cerebral blood flow.

	Item
1	$PaCO_2$
2	PaO_2
3	Blood viscosity
4	Intercranial pressure
5	Mean arterial pressures
6	Central venous pressure
7	Drugs

The notion that 50 mmHg is a safe lower limit for MAP on CPB appears to reflect the notion that this is the lower limit at which autoregulation of the cerebral circulation occurs. Within the limits of autoregulation, flow is driven by cerebral metabolic rate rather than perfusion pressure. Cerebral metabolic rate is influenced (amongst other things) by hypothermia. In reality, the range of cerebral autoregulation varies between individuals, and studies show enormous between-patient variability in blood flows at any given pressure. The concept of a lower range of 50 mmHg seems to have been predicated on one or two older studies which have been subject to serious methodological criticism.

Acid base management is integral to any discussion of perfusion on bypass. pH is defined as the negative logarithm of the Hydrogen ion concentration ([H+]), or pH = −log [H+]. Electrochemical neutrality is defined as the point where [H+] = [OH−]:

- Neutral pH (pN) is 7.00 at 25°C where $[H^+] = [OH^-] = 1 \times 10^{-7}$ mole/L.
- For water, At 37°C pN is 6.80; at 17°C pN is 7.14.
- At 37°C intra-cellular pN is 6.80 and extra-cellular pN is 7.4 (the pN of blood).

During cooling of aqueous solutions, both $[H^+]$ and $[OH^-]$ decrease because the spontaneous dissociation of water decreases. Homeotherms maintain their temperature despite changes in their environment. Poikilotherms' temperature changes with changes in the environmental temperature. Most poikilotherms tend to maintain intracellular pH near pN over a wide range of temperatures. As they cool, intra- and extra-cellular pH increases and so does pN (much as for water).

The constituent of proteins thought responsible for the remarkably constant intra-cellular balance between $[H^+]$ and $[OH^-]$ as temperature varies is histidine. The degree of dissociation of the imidazole group of histidine (approximately 0.55—called "α") doesn't change appreciably with temperature; instead, the pKa of the imidazole *does* vary. Humans appear to maintain α-stat physiology. This includes keeping the CO_2 *content* of the blood constant with varying temperature, because a change in CO_2 content would alter α.

Henry's law states that the amount of gas in a solution is proportional to its partial pressure; as temperature drops, the partial pressure of CO_2 decreases, but its solubility increases, so the total content of CO_2 remains constant and so does α.

The object in α-stat management of CPB is to keep pH at 7.4 and pCO_2 at 40 mmHg as measured at 37°C. If the same samples were corrected to the patient's temperature, these results would indicate a respiratory alkalosis (pH high, pCO_2 low). pH-stat involves aiming for the same targets *after* correction for temperature; this requires the addition of pCO_2 and is a more acidic technique. Most enzyme reactions have pH optima that follow the predictions of α-stat theory. Therefore metabolic rate would be expected to reduce with pH-Stat, and this is thought to be the mechanism by which hibernating species conserve oxygen (they follow pH-stat acid base physiology). However, in a study by Murkin discussed below (18), cerebral metabolic rate did not vary between pH-stat and α-stat management, so the former approach produced more flow for a given metabolic rate (see below). Other studies have shown lower metabolic rates with pH-stat, but at the temperatures typically used for adult CPB, the weight of current evidence suggests that there is very little difference in metabolic rate between the two approaches.

The relationship between cerebral blood flow and perfusion pressure depends on whether α-stat or pH-stat management of acid base is used. Murkin et al. has demonstrated that cerebral blood flow autoregulation is better maintained in presence of α-stat management (18). For most given cerebral perfusion pressures, cerebral blood flow is higher with pH-stat management of CPB (which may be a good or a bad thing—see above). At some temperatures this relationship reverses.

Bashein et al. showed that at moderate hypothermia, carbon dioxide management during cardiopulmonary bypass has no clinically significant effect on either neurobehavioural or cardiac outcome (19). In a study by Stephan and co-workers, new neurological deficits were more common in pH-stat patients. In a study by Patel and co-workers, the conclusion was "patients receiving alpha-stat management had less disruption of cerebral autoregulation during cardiopulmonary bypass, accompanied by a reduced incidence of postoperative cerebral dysfunction." (20). This clinical advantage was consistent with findings in another study by Murkin (21).

How then should one control blood pressure on CPB? Dilators and constrictors seem to be more popular than alterations in flow rate, however we have a very poor understanding of the regional effects of these drugs. Given the forgoing discussion, it seems that the outcome of changing pressure by these manipulations is even less certain.

REFERENCES

1. Gold, JP, Williams-Russo P, Szatrowski TP, et al., Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. JTCVS 1995;110:1302–11, discussion 1311–4.
2. Roach GW, Kanchuger M, Manzano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med. 1996;335:1857–63.
3. Barbut D, Grassineau D, Lis E, et al. Posterior distribution of infarcts in strokes related to cardiac operations. Ann Thorac Surg. 1998;65:1656–9.
4. Likosky DS, Marrin CAS, Caplan LR, et al. Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. Stroke. 2003;34:2830–4.
5. Stockard JJ, Bickford RG, Myers RR, et al. Hypotension-induced changes in cerebral function during cardiac surgery. Stroke. 1974;5:730–46.
6. Murkin JM. Pro: tight intraoperative glucose control improves outcome in cardiovascular surgery. J Cardiothor Vasc Anesth. 2000;14:475–8.
7. Schmidt M, Scheunert T, Steinbach G, et al. Hypertension as a risk factor for cerebral injury during cardiopulmonary bypass. Protein S100B and transcranial Doppler findings. Anaesthesia. 2001;56:733–8.
8. Hartman GS, Yao FS, Bruefach M 3rd, et al. Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: a prospective study. Anesthesia & Analgesia. 1996;83:701–8.
9. Mitchell SJ, Pellett O, Gorman DF. Cerebral protection by lidocaine during cardiac operations. Ann Thorac Surg. 1999;67:1117–24.
10. Mora CT, Henson ME, Weintraub WS, et al. The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. J Thorac Cardiovasc Surg. 1996;112:514–22.
11. Stockard JJ, Bickford RG, Schauble JF. Pressure-dependent cerebral ischemia during cardiopulmonary bypass. Neurology. 1973;23:521–9.

12. Brown WR, Moody DM, Challa VR, Stump DA, Hammon JW. Longer duration of cardiopulmonary bypass is associated with greater numbers of cerebral microemboli. Stroke. 2000;31:707–13.
13. Ergin MA, Griepp EB, Lansman SL, et al. Hypothermic circulatory arrest and other methods of cerebral protection during operations on the thoracic aorta. Journal of Cardiac Surgery. 1994;9:525–37.
14. Mitchell SJ, Willcox T, Gorman DF. Bubble generation by the medtronic maxima hard shell adult reservoir in cardiopulmonary bypass circuits. Undersea and Hyperbaric Medicine. 1996;23:A12.
15. Willcox TW, Mitchell SJ, Gorman DF. Venous air in the bypass circuit: a source of arterial line emboli exacerbated by vacuum-assisted drainage. Ann Thorac Surg. 1999;68:1285–9.
16. Tachakra SS. Distribution of skin petechiae in fat embolism rash. Lancet. 1976;1:284–5.
17. Fang WC, Helm RE, Krieger KH, et al. Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation. 1997;96:II-194–9.
18. Murkin JM, Farrar JK, Tweed A, McKenzie NF, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of PaCO2. Anesthesia & Analgesia. 1987;66:825–32.
19. Bashein G, Townes BD, Nessly ML, et al. A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. Anesthesiology. 1990;72:7–15.
20. Patel RL, Turtle, MR, Chambers DJ, et al. Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuropsychologic outcome in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 1996;111:1267–79.
21. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. J Thorac Cardiovasc Surg. 1995;110:349–62.

Conducting Clinical Trials

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EVIDENCE BASED MEDICINE

Sackett has defined evidence based medicine (EBM) as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research." (1). Sources of external clinical evidence include clinical research (of which randomized controlled trials are only a part), research from basic science, and research which synthesises expert opinion. A hierarchy has been proposed (Table 1) for use in evaluating this evidence.

Table 1. Hierarchies of evidence defined by Eccles et al. (2)

Category of Evidence
Ia: evidence from meta-analysis of randomised controlled trials
Ib: evidence from at least one randomised controlled trial
IIa: evidence from at least one controlled study without randomisation
III: evidence from non-experimental discriptive studies; such as comparative studies, correlation studies and case-control studies
IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Since more weight is placed on the results of the randomized controlled trial (RCT) than on expert opinion, it follows that a basic understanding of clinical research is relevant to all clinicians who wish to practice EBM. Does it also follow that all clinicians should undertake research? Research is expensive in time, and often also in other resources. Our patients are our most precious resource. The world literature has been flooded with reports of studies varying from excellent to un-interpretable. Separating the meaningful from the meaningless and synthesizing these data into useful information has become a major challenge. In fact, a whole industry has arisen around systematic reviews of clinical studies (Box 1). Unfortunately, systematic reviews (with or without meta-analysis) can only be as good as the trials they review.

THE VARIABLE QUALITY OF PUBLISHED RESEARCH

A persistent problem with the interpretation of the results of research relates to the variable quality of the research. This may seem surprising, at least in respect of peer reviewed journals. However, the assumption that the process of editorial peer review ensures adequate quality in either the conduct or the reporting of research seems to be unfounded. In 1983, Bailar and Patterson identified that part of the problem of poor quality in published research was a lack of empirical research into the peer review and editorial processes at the heart of medical literature, and called for studies to be done on these processes (3). Editors at JAMA responded by convening a conference at which the results of such research could be presented. By 2002 nearly 200 papers per year dealt with this subject. However, in an editorial on the fourth such conference Rennie quoted the following comment made after the third conference and indicated that it still applied.

". . . there are scarcely any bars to eventual publication. There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of