Editorials

What exactly is the strong ion gap, and does anybody care?

The landscape of critical illness is littered with gradients and gaps. Some enter our consciousness only rarely. Others are discussed every day at the bedside and their trends followed with great interest. Examples include the alveolar-arterial PO_2 gradient,[1] the veno-arterial PCO_2 gradient,[1] the pulmonary diastolic - PAoP gradient,[2] the arterial to mucosal pH gradient,[3] the lactate gap,[4] the regional-arterial PCO_2 gap,[1] the osmolal gap,[5] the plasma anion gap (AG),[6] the corrected anion gap (AGc)[7] and the urinary anion gap.[8] Some gaps can reveal hidden pathophysiology, resetting the diagnostic and therapeutic course. Others are less rewarding. Tracking the arterial to mucosal pH gradient can seem more akin to interrogation of tea leaves or goat entrails.

There is a newcomer waiting to join this motley crew - the strong ion gap (SIG).[9] Its preferred job description is as a scanning tool for unmeasured (or unsuspected) ions, particularly anions, and perhaps also as a prognostic index in critical illness. The question is 'but what's in it for us?' Does the critical care community need another gap, and if so can the SIG tell us anything that other acid-base scanning tools like the AG or AGc, or even a global index like standard base excess (SBE), cannot? The next couple of pages are an attempt to answer these questions. In doing so we will need to conduct yet another foray into the physical chemical world of Peter Stewart.

Stewart's principles in brief[10,11]

Stewart showed that the interplay between three independent variables, PCO_2, the total concentration of non-volatile weak acid (A_{TOT}) and the strong ion difference (SID), determines the status of pH, $[HCO_3^-]$ and other dependent variables in body fluids.

SID

Strong ions are chemical entities that remain fully dissociated at physiologic concentrations, under all acid-base conditions compatible with life. Quantitatively, their unionised concentrations are so minute they can be disregarded. The principal strong cations in plasma are Na^+ and K^+, and the principal strong anion is Cl^-. Organic acid anions with pKa < 4, such as lactate and ketoacids, also behave as strong anions. SID = [strong cations] - [strong anions]. In plasma there is a surfeit of strong cations, so that plasma SID is approximately 42 mEq/L.

A_{TOT}

Body fluid compartments have varying concentrations of non-volatile (i.e. non-CO_2) weak acids (HA). In plasma these consist of albumin and inorganic phosphate. Non-volatile weak acids dissociate in body fluids as follows:

$$HA \leftrightarrow H^+ + A^-$$

The total concentration of non-volatile weak acid in any compartment is termed A_{TOT}, where $A_{TOT} = [HA] + [A^-]$. Although $[A^-]$ varies with pH, A_{TOT} does not, and as such is an independent variable. Raising and lowering A_{TOT} while holding SID constant cause a metabolic acidosis and alkalosis respectively. Lowering and raising plasma SID while clamping A_{TOT} cause a metabolic acidosis and alkalosis respectively.

Weak ions

The SID space is filled by weak ions, one of which is A^-. The only other quantitatively important weak ion is HCO_3^-, but there are also minute concentrations of CO_3^{2-}, OH^-, and H^+. To preserve electrical neutrality their net charge must always equal SID.

SID can thus be calculated conveniently as $[HCO_3^-] + [A^-]$), a value which used to be called the 'buffer base', and is now often termed the 'effective' SID, or SIDe (Table 1). When SID is calculated more laboriously from measured plasma strong ion concentrations, it is termed the 'apparent' SID, or SIDa (Table 1).

Unmeasured strong anions

Accumulations of unmeasured strong anions reduce SID and are important causes of metabolic acidosis. Examples of endogenous strong anions which can accumulate include lactate in sepsis and shock states,[12] acetoacetate and beta-hydroxybutyrate in ketoacidosis,[13] and D-lactate in short bowel syndrome.[14] There are many others.[15] Strong anions can arise from exogenous sources, Examples include pyroglutamate,[16] salicylate,[17] formate,[18] and glycolate.[19,20] Exogenous strong anions behave similarly from an acid-base perspective, but often have a propensity for direct toxicity.

Early detection of accumulated strong anions would doubtless facilitate diagnostic speed. On occasion it might save lives. Methanol and ethylene glycol poisoning are cases in point, where formate or glycolate/oxalate accumulation can be prevented by prompt administration of 4-methylpyrazole,[21] or institution of haemodialysis.[18-20,22] However, Cl^- is still the only directly measured strong anion reported on a routine plasma biochemical profile. Plasma L-lactate

Table 1. Some acid-base calculations

Name	*Calculation*
$[A^-]$	[Albumin] × (0.123 × pH - 0.631) + [Phosphate] × (0.309 × pH -0.469)
$[HCO_3^-]$	$0.0301 \times PCO_2 \times 10^{(pH - 6.1)}$
AG*	$([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$
AGc**	AG + 0.25 × (40 - [Albumin])
SIDe	$[A^-] + [HCO_3^-]$
SIDa	$[Na^+] + [K^+] + [Ca^{++}] + [Mg^{++}] - [Cl^-]$ - [L-lactate] - [urate]
SIG	SIDa - SIDe

AG = anion gap, AGc = corrected anion gap, SIDe = effective strong ion difference, SIDa = apparent strong ion difference, SIG = strong ion gap. *$[K^+]$ omitted in many laboratories. **Assumes normal [Albumin] = 40 g/L

measurements are now more common, mainly with point of care instruments, but beta-hydroxybutyrate and salicylate assays are never forthcoming without specific requests, and hospital laboratories find rapidly accessible assays for pyroglutamate, glycolate, oxalate or formate either cost ineffective or unavailable. A simple reliable scanning tool for unmeasured strong anions would therefore be a useful part of our diagnostic armamentarium. In which case, how does the SIG compare with the existing contenders, SBE, the AG and the AGc?

SBE

Indices of overall metabolic acid-base status seem unlikely to do the job well. SBE is the best of these.[22] It represents the change in extracellular SID needed to normalise metabolic acid-base status at the existing A_{TOT}.[23] However, as a signal for unmeasured anions, SBE suffers from considerable background noise. For example, simple narrowing of the gap between $[Cl^-]$ and $[Na^+]$ reduces SID and thus SBE. This is a common phenomenon, particularly with the widespread use of low SID resuscitation fluids.[24-26] Of note, a low A_{TOT} or reductions in plasma $[Cl^-]$ oppose the fall in SBE caused by accumulated strong ions, reducing sensitivity. With all these factors operating, SBE should be an unreliable scanning tool for unmeasured strong anions, unless they are present in high concentrations.

AG

The AG looks to be a step forward. It is normally calculated as $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$, although $[K^+]$ is omitted in many laboratories (Table 1). By the principle of electrical neutrality, the AG really quantifies [unmeasured anions] - [unmeasured cations], both strong and weak. The AG would thus normally be elevated in the presence of unmeasured anions and reduced by unmeasured cations. Although there can be a wide variety of unmeasured ions, in health the bulk of the AG is made up of weak anions - the $[A^-]$ component of A_{TOT} (i.e. the negative charge on albumin and phosphate). As a result, the AG response to unmeasured strong anions can easily be blurred by A_{TOT} fluctuations, which alter $[A^-]$ directly, and severe pH disturbances, which alter the $[A^-]$ component of A_{TOT} (Table 2).[7,27,28]

However, as also shown in Table 2, the AG is sensitive to altered $[Ca^{++}]$[29] and $[Mg^{++}]$,[30] lithium carbonate administration,[31] THAM administration and high concentrations of anionic and cationic globulins.[32] Unfortunately, these all erode AG sensitivity and specificity when scanning for unmeasured strong anions.[33,34] Despite these deficiencies the AG should still perform better than SBE. Which makes it surprising that in the best available comparison (scanning for plasma L-lactate > 5 mmol/L), it was no better than base excess.[35] Areas under the ROC curve for both were approximately 0.85.

AGc

The AGc[7,36] was devised to overcome just one AG deficiency, albeit a major one, namely susceptibility to variations in plasma A_{TOT} (Table 1). However, for a few reasons the correction is fairly rough. First, it adjusts for albumin fluctuations only, not allowing for phosphate offsets at all. Except in severe hyperphosphataemia this makes little difference. Second, it attributes a fixed negative charge to albumin, making no adjustment for pH effects on imidazole groups. Again this can be shown to be a minor source of error, except in severe alkalaemia.

Finally, there is a theoretical objection. Although 'correcting' derived variables such as the AG has intuitive merit, the usual laboratory reference ranges (derived from 'uncorrected' AG values) are still applied. Ideally 'corrected' values should be used to derive 'corrected' reference ranges. Because the reference population is healthy, this difference should also be small.

Despite all this, the AGc should be an advance on its uncorrected version, particularly in critical illness when plasma [albumin] varies widely and is often greatly reduced. It would be good to prove this. For reasons that are unclear, an opportunity was lost in the recent study by Rocktaeschel and co-workers.[35]

Table 2. Comparison of anion gap (AG), corrected anion gap (AGc) and strong ion gap (SIG)

	AG	*AGc*	*SIG*
Unmeasured strong anions (eg lactate, keto-acids)	Increased	Increased	Increased
Unmeasured weak anions (e.g. polygelinate, IgA myeloma)	Increased	Increased	Increased
Unmeasured strong cations (e.g. lithium)	Reduced	Reduced	Reduced
Unmeasured weak cations (e.g. $THAMH^+$, IgG myeloma)	Reduced	Reduced	Reduced
Bromism, hyperlipidemia (Positive $[Cl^-]$ measurement bias)	Reduced	Reduced	Reduced
Hypernatraemia (Negative $[Na^+]$ measurement bias)	Reduced	Reduced	Reduced
[Pi]	⇑ raises ⇓ lowers	⇑ raises ⇓ lowers	No effect
pH	⇑ raises ⇓ lowers	⇑ raises ⇓ lowers	No effect
$[Ca^{++}]$ and $[Mg^{++}]$	⇑ lowers ⇓ raises	⇑ lowers ⇓ raises	No effect
[Albumin]	⇑ raises ⇓ lowers	No effect	No effect

SIG

The SIG concept, first hit upon by Figge and colleagues,[37] exploits the fact that there are two ways to determine SID, namely SIDa, calculated by summation of individual strong anion and cation concentrations, and SIDe, calculated as ($[A^-]$ + $[HCO_3^-]$) (Table 1). In healthy individuals inhabiting an error-free world, SIG, which is the difference between the two, would be zero. Unmeasured strong anions would reveal their presence by increasing SIDa, giving SIG a positive value.

However, a number of realities conspire against this ideal. Firstly, like the AG, the SIG is a quantification of [unmeasured anions] - [unmeasured cations], both strong and weak. Its advantage over AG and AGc is that the unmeasured list is shorter (Table 1). This theoretically insulates SIG from variations in A_{TOT}, pH, [L-lactate], $[Ca^{++}]$ and $[Mg^{++}]$ (Table 2). However, it still leaves SIG vulnerable to unmeasured strong cations like lithium, and unmeasured weak anions such as polygelinate (from gelatin-based colloid preparations), weak cations such as $THAMH^+$, and the anionic and cationic bands of multiple myeloma (Table 2). A further disadvantage is that each extra analyte brings with it its own imprecision. As a result, the confidence intervals around SIG values due to measurement variability alone are likely to be quite wide and should exceed ± 7 mEq/L.[38] By comparison, the confidence intervals for AG, when incorporating both measurement and population variability, are generally only ± 5 mEq/L.

Systematic bias has also been noticed. In other words it should not be assumed that the normal reference range for SIG is centred on zero. The 'normal' SIG at this author's hospital, calculated by inserting local mid reference-range values in the SIG equation, comes to around 3.7 mEq/L. Small concentrations of keto-acids and other metabolic anions no doubt can contribute to some extent, but do not explain a positive SIG of this size. (Readers are invited to perform this exercise, using published values from their own hospital laboratories). Similar positive SIG bias has cropped up in other parts of the world,[38,39] but not everywhere.[9,37]

This does not mean that regions where the mean SIG is strongly positive are populated by individuals harbouring exotic anions. More likely there is systematic bias in one or more components of the SIG determination, due to locally adopted measurement technologies and variations in analytic reference standards. It is widely recognised that when different technologies measure the same thing they produce different reference values. Unless this is taken into account, results can be misinterpreted and diagnostic conclusions skewed.[40] If SIG is to find clinical application, individual laboratories will need to calibrate on site against a local population. The good news is that systematic bias, unlike imprecision, can be factored out, once recognised.

The main question, given the likely imprecision and residual background noise, is whether the SIG is really any better at detecting unmeasured ions. Unfortunately, there are no published data to provide the answer. In Rocktaeschels's study[35] the base excess gap,[41] a close cousin of SIG in which L-lactate remains an unmeasured anion, was no more useful than the AG at detecting plasma [L-lactate] > 5 mmol/L. The area under the ROC curve for each was around 0.85.[35] For what it is worth, this editorialist has unpublished data which may shed further light. Using 296 paired data-sets from one ICU, an [L-lactate] threshold of 2.5 mmol/L, and SIG values calculated without L-lactate, there was little difference in the hyperlactaemia scanning power of the AG, SIG and base excess gap. Areas under the ROC curve were 0.82, 0.85, and 0.84 respectively. Interestingly, the area

under the ROC curve for SBE was only 0.36, more in line with the background noise transmitted through SBE in sick patients.

The main danger with highly processed indices like the SIG and the base excess gap is over-interpretation. There has been speculation about unsuspected anions[9,42] and even unidentified cations[41] in critical illness, based on positive and negative deviations or significant differences in base excess gap or SIG values. Although these possibilities cannot be ruled out, particularly in the Kaplan study,[42] both SIG and the base excess gap are inherently imprecise. Note also that both indices contain pH-based calculations of weak acid behaviour. Small systematic inaccuracies if present will be magnified in sicker patients with prominent acid-base disturbances. It is wise to remember the tidal wave that grew out of apparent delivery-dependent oxygen consumption and presumed covert oxygen debt,[43-49] until someone thought of mathematical coupling.[50-52]

Similar comments apply to prognostic power. A couple of studies have produced data suggesting that the SIG [42] or the base excess gap[53] are more predictive of mortality, perhaps because hidden ions are reflected in their values. However, two other well-conducted studies do not support that contention.[35,39] Rocktaeschel and colleagues conclude that indices for unmeasured anions are too closely correlated for any one to outshine the rest.[35] This editorialist concurs with that view.

So where does that leave us? Will SIG fill a unique and valuable niche? Can it give us information than its rivals cannot? The jury is still out, but I think their answer will probably be 'no'. Watch this space.

Dr. T. J. Morgan
Adult Intensive Care Units
Mater Misericordiae Hospital, South Brisbane
QUEENSLAND 4101

REFERENCES

1. Morgan TJ, Venkatesh B. Monitoring oxygenation. In: Bersten AD, Soni N, editors. Oh's Intensive Care Manual. Oxford: Butterworth-Heinemann: 2003. P. 95-106
2. Morgan TJ. Haemodynamic monitoring. In: Bersten AD, Soni N, editors. Oh's Intensive Care Manual. Oxford: Butterworth-Heinemann; 2003. P. 79-94
3. Gomersall CD, Joynt GM, Ho KM, Young RJ, Buckley TA, Oh TE. Gastric tonometry and prediction of outcome in the critically ill. Arterial to intramucosal pH gradient and carbon dioxide gradient. Anaesthesia 1997;52:619-623.
4. Venkatesh B, Morgan T, Garrett P. Uses of error: Measuring the lactate gap. Lancet 2001;358:1806.
5. Schelling JR, Howard RL, Winter SD, Linas SL. Increased osmolal gap in alcoholic ketoacidosis and lactic acidosis. Ann Intern Med 1990;113:580-582.
6. Emmet M, Narins RG. Clinical use of the anion gap. Medicine 1977;56:38-54.
7. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. Crit Care Med 1998;26:1807-1810.
8. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urine anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med 1988;318:594-599.
9. Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 1995;10:51-55.
10. Stewart PA. How to understand acid-base. In: Stewart PA (editor). A quantitative acid-base primer for biology and medicine. Elsevier, New York: 1981. P. 1-286.
11. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444-1461.
12. DeBacker D. Lactic acidosis. Intensive Care Med 2003;29:699-702.
13. DeFronzo RA, Matsuda M, Barrett EJ. Diabetic ketoacidosis. Diabetes Rev 1994;2:209-238.
14. Oh MS, Phelps KR, Traube M, et al. D-Lactic acidosis in a man with the short-bowel syndrome. New Engl J Med 1979;301:249-252
15. Worthley LIG. Acid-base balance and disorders. In: Bersten AD, Soni N, editors. Oh's Intensive Care Manual. Oxford: Butterworth-Heinemann: 2003. P. 873-883.
16. Dempsey GA, Lyall HJ, Corke CF, Scheinkestel CD. Pyroglutamic acidemia: a cause of high anion gap metabolic acidosis. Crit Care Med 2000;28:1803-1807.
17. Chapman BJ, Proudfoot AT. Adult salicylate poisoning: deaths and outcome in patients with high plasma salicylate concentrations. Q J Med 1989;72:699-707.
18. Gonda A, Gault H, Churchill D and Hollomby D. Hemodialysis for methanol intoxication. Am J Med 1978;64:749-757.
19. Peterson CD, Collins AJ, Himes MJ, Bullock ML, Keane WF Ethylene glycol poisoning. N Engl J Med 1981;304:21-23
20. Jacobsen D, Hewlett TP, Webb R, Brown ST, Ordinario AT, McMartin KE. Ethylene glycol intoxication: evaluation of kinetics and crystalluria. Am J Med 1988;84:145-152
21. Baud FJ, Galliot M, Astier A, et al. Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. N Engl J Med 1988;319:97-100.
22. Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anesth Scand 1995;39: Suppl 107, 123-128.
23. Schlichtig R, Grogono AW, Severinghaus JW. Current status of acid-base quantitation in physiology and medicine. Anesthesiology Clinics of North America 1998;16:211-233.
24. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90:1265-1270.
25. McFarlane C, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia 1994;49:779-781.

26. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999;90:1247-1249.
27. Figge J, Rossing TH, Fencl V. The role of serum proteins in acid-base equilibria. J Lab Clin Med 1991;117:453-467.
28. Madias NE, Ayus JC, Adrogue HJ. Increased anion gap in metabolic alkalosis: the role of plasma protein equivalency. N Engl J Med 1979;300:1421-1423.
29. Oster JR, Gutierrez R, Schlessinger FB, Taylor A, Federman DG, Vaamonde CA. Effect of hypercalcemia on the anion gap. Nephron 1990;55:164-169.
30. Clark BA, Brown RS. Unsuspected morbid hypermagnesemia in elderly patients. Am J Nephrol 1992;12:336-343.
31. Kelleher SP, Raciti A, Arbeit LA. Reduced or absent serum anion gap as a marker of severe lithium carbonate intoxication. Arch Intern Med 1986;146:1839-1840.
32. Goldstein RJ, Lichtenstein NS, Souder D. The myth of the low anion gap. JAMA 1980;243:1737-1738.
33. Salem MM, Mujais SK. Gaps in the anion gap. Arch Int Med 1992;152:1625-1629.
34. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP. Low sensitivity of the anion gap as a screen to detect hyperlactaemia in critically ill patients. Crit Care Med 1991;19:130-131
35. Rocktaeschel J, Morimatsu H, Uchino S, Bellomo R. Unmeasured anions in critically ill patients: Can they predict mortality? Crit Care Med 2003;31:2131-2136.
36. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000;162:2246-2251.
37. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. J Lab Clin Med 1992;120:713-719.
38. Story DA, Poustie S, Bellomo R. Comparison of three methods to estimate bicarbonate in critically ill patients: Henderson-Hasselbalch, enzymatic, and strong ion gap. Anaesth Intensive Care 2001;29:585-590.
39. Cusack RJ, Rhodes A, Lochead P, et al. The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. Intensive Care Med 2002;28:864-869.
40. Morimatsu H, Rocktaschel J, Bellomo R, Uchino S, Goldsmith D, Gutteridge G. Comparison of point-of-care versus central laboratory measurement of electrolyte concentrations on calculations of the anion gap and the strong ion difference. Anesthesiology 2003;98:459-460.
41. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. J Crit Care 1993;8:187-197.
42. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med 2004;32:1120-1124.
43. Edwards JD, Brown GC, Nightingale P, Slater RM, Faragher EB. Use of survivors' cardiorespiratory values as therapeutic goals in septic shock. Crit Care Med 1989;17:1098-1103.
44. Dhainut FJ, Edwards JD, Grootendorst AF, et al. Practical aspects of oxygen transport: Conclusion and recommendations of the round table conference. Intensive Care Med 1990;16:S179-S180.
45. Alia I, Esteban A, Gordo F, et al. A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. Chest 1999;115:453-461.
46. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992;102:216-220.
47. Gattinoni L, Brazzi L, Pelosi P, et al for the SvO_2 Collaborative Group. A trial of goal-orientated hemodynamic therapy in critically ill patients. N Engl J Med 1995;333:1025-1032.
48. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-1722.
49. Yu M, Levy MM, Smith P, Takiguchi SA, Miyasaki A, Myers SA. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: A prospective, randomized, controlled study. Crit Care Med 1993;21:830-838.
50. Phang PT, Cunningham KF, Ronco JJ, Wiggs BR, Russell JA. Mathematical coupling explains dependence of oxygen consumption on oxygen delivery in ARDS. Am J Respir Crit Care Med 1994;150:318-323.
51. Hanique G, Dugernier T, Laterre PF, et al. Evaluation of oxygen uptake and delivery in critically ill patients: A statistical reappraisal. Intensive Care Med 1994;20:19-26.
52. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 1993;269:3024-3029.
53. Balasubramanyan N, Havens PL, Hoffman GM. Unmeasrued anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. Crit Care Med 1999;27:1577-1581.

Oxygen therapy for acute illness: reasoned or ritual?

Oxygen therapy is often used in the acutely ill patient based on a belief that individuals at risk of hypoxia are benefited by oxygen and that oxygen is without adverse effects. However, while life cannot be sustained without oxygen, there is surprisingly little evidence to support its routine use in the critically ill patient outside its role in cardiopulmonary resuscitation where both an urgent increase in haemoglobin saturation as well as cardiac output are required to deliver oxygen rapidly to the brain and heart.

Normal human arterial oxygen tension at sea level varies between 80 - 100 mmHg and corresponds to a saturation of 96 - 97%.[1] The oxyhaemoglobin dissociation curve reveals a haemoglobin saturation that is

altered little while the oxygen tension falls from 100 mmHg to 60 mmHg, thereby maintaining the arterial oxygen content in the presence of a low ambient pressures or pulmonary disease. At low oxygen pressures the curve demonstrates an oxygen tension which is maintained while the saturation falls, thereby sustaining a pressure gradient necessary to diffuse oxygen from blood to mitochondria.[2] As long as there is an effective pressure gradient, oxygen will diffuse into tissues with mitochondrial cytochrome c oxidase reducing oxygen to water at oxygen levels as low as 2.25 mmHg.[3] At mitochondrial oxygen tensions above 7.5 mmHg oxygen uptake is increased, an effect which is most likely due to an increase in oxygen radical production.[3] When a progressive reduction in inhaled oxygen is applied, anaerobic metabolism with increasing blood lactate levels appears to occur in the human at an arterial blood haemoglobin oxygen saturation (SaO_2) of 40% or PaO_2 of 23 mmHg,[4-6] a value which is rarely achieved with lung injury.

Tissue oxygen delivery depends on cardiac output, haemoglobin concentration and haemoglobin oxygen saturation and a reduction of up to 50% in haemoglobin concentration in the critically ill patient has been reported to be beneficial,[7] although many clinicians do not tolerate a saturation reduction in any patient of more than 10%. When pulmonary shunt produces an SaO_2 of 85% with an inspired oxygen concentration (F_IO_2) of 0.3, an increase in F_IO_2 to 1 will increase the SaO_2 by 8% and oxygen content by 9%.[8] The resultant increase in oxygen delivery could easily be accomplished by a similar percentage increase in cardiac output or haemoglobin with no change in F_IO_2.

Of the pulmonary disorders that cause a low SaO_2 (e.g. hypoventilation, low ventilation/perfusion ratio, intrapulmonary shunt, diffusion defect) some increase in SaO_2 occurs with an increase in inhaled oxygen, although none are cured. Oxygen therapy may even delay diagnosis and corrective therapy.[2]

On the other hand, high inspired oxygen levels have been repeatedly identified as a source of acute lung injury,[9-11] atelectasis,[12] and adverse central nervous system effects.[13] In one prospective, randomised double-blind controlled study of patients with uncomplicated myocardial infarction, oxygen, at 6 L/min for 24 hours, was not associated with any reduction in mortality and may have been detremental.[14] In a study of patients with acute stroke, oxygen administration at 3 L/min through nasal cannulae was not associated with any benefit.[15] Postoperative increase in ventilation/perfusion mismatch is increased if extubation is preceded by a short period of 100% oxygen[16,17] and while one prospective, randomised study of patients undergoing colorectal surgery reported a reduction in the incidence of surgical wound infections from 11.2% to 5.2%, using 80% oxygen compared with 30% oxygen interoperatively and two hours postoperatively,[18] another study of patients undergoing major intraabdominal surgery found that this therapy was associated with an increase in the incidence of surgical site infections (e.g. 11.3% vs 25%).[19]

A lack of correlation between arterial oxygen levels and long term outcome has also been demonstrated in the ARDS network study where low and traditional tidal volumes were compared. Those who received the 6 mL/kg of predicted body weight tidal volume during mechanical ventilation had a lower mean PaO_2 than those randomised to receive a higher tidal volume, yet had a statistically lower mortality rate.[20] The absence of a relationship between arterial oxygen level and mortality was also found in a multicentre, randomised, placebo-controlled study of non-sepsis ARDS patients where nitric oxide at 5 ppm up to 28 days was not associated with any significant effect on duration of ventilatory support or mortality, although there was a significant increase in PaO_2.[21] Even in the two recent multicentre, double-blind, randomised trials in ARDS patients treated with recombinant surfactant protein C-based surfactant, the arterial oxygenation was higher in the treated patients compared with the untreated patients without any change in mortality.[22]

Nonetheless, in COPD patients whose disease is stable with maximum medical therapy and who have a PaO_2 < 55 mmHg (< 7.4 kPa), long-term oxygen therapy (LTOT) for more than 15 hours per day prolongs life expectancy, improves sleep, cognitive functions and prevents progression of hypoxic pulmonary hypertension,[23,24] although LTOT appears not to improve mortality in patients with COPD and a PaO_2 between 56 - 65 mmHg.[25]

Hypoxia is a feature that requires a clinical diagnosis and specific treatment which may include antibiotics, anticoagulation, corticosteroids, bronchodilators, diuretics, ACE inhibitors, etc, rather than just an increase in inhaled oxygen. As there are no human data that define the optimal F_IO_2 and SaO_2 in critically ill patients, a wide variation of SaO_2 tolerance and F_IO_2 prescription is often found in clinical practice.[26-29] Perhaps, oxygen should be thought of in the same light as any resuscitation manoeuvre (e.g. external cardiac massage, mechanical ventilation) and prescribed to achieve a PaO_2 > 55 mmHg but < 80 mmHg (SaO_2 between 85% and 95%) while the disorder causing the hypoxia is diagnosed and definitive therapy takes effect.

Dr. L. I. G. Worthley
Department of Critical Care Medicine
Flinders Medical Centre
SOUTH AUSTRALIA 5042

REFERENCES
1. Roughton FJW, Severinghaus. JW. Accurate determination of O2 dissociation curve of human blood above 98.7% saturation with data on O2 solubility in unmodified human blood from 0º to 37º. J Appl Physiol 1973;35:861-869.
2. Downs JB. Has oxygen administration delayed appropriate respiratory care? Fallacies regarding oxygen therapy. Respir Care 2003;48:611-620.
3. Gnaiger E. Oxygen conformance of cellular respiration. A perspective of mitochondrial physiology. Adv Exp Med Biol 2003;543:39-55.
4. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA 1993;270:1724-1730.
5. Snyder JV, Carroll GC. Tissue oxygenation: A physiologic approach to a clinical problem. Curr Probl Surg 1982;19:650-719.
6. Eldridge F. blood lactate and pyruvate in pulmonary insufficiency. N Engl J Med 1966;274:878-883.
7. Hébert PC, Wells G, Blajchman MA, et al and the Transfusion Requirements in Critical Care (TRICC) Investigators for the Canadian Critical Care Trials Group. A multicenter, randomised, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409-417.
8. Downs JB, Smith RA. Increased inspired oxygen concentration may delay diagnosis and treatment of significant deterioration in pulmonary function. Crit Care Med 1999;27:2844-2846.
9. Winter PM, Smith G. The toxicity of oxygen. Anaesthesiology 1972;37:210-241.
10. Beckett WS, Wong ND. Effect of normobaric hyperoxia on airways of normal subjects. J Appl Physiol 1988;64:1683-1687.
11. Crapo JD, Hayatdavoudi G, Knapp MJ, Fracica PJ, Wolfe WG, Piantadosi CA. Progressive alveolar septal injury in primates exposed to 60% oxygen for 14 days. Am J Physiol 1994;267(6 Pt 1):L797-L806.
12. Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100 per cent O2. J Clin Invest 1974;54:54-68.
13. Yusa T, Beckman JS, Crapo JD, Freeman BA. Hyperoxia increases H_2O_2 production by brain in vivo. J Appl Physiol 1987;63:353-358.
14. Rawles JM, Kenmure ACF. Controlled trial of oxygen in uncomplicated myocardial infarction. Br Med J 1976;1:1121-1123.
15. Rønning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. Stroke 1999;30:2033-2037.
16. Benoit Z, Wicky S, Fischer JF, et al.The effect of increased FIO(2) before tracheal extubation on postoperative atelectasis. Anesth Analg 2002;95:1777-1781.
17. Loeckinger A, Kleinsasser A, Keller C, et al. Administration of oxygen before tracheal extubation worsens gas exchange after general anesthesia in a pig model. Anesth Analg 2002;95:1772-1776.
18. Greif R, Akca O, Horn EP, Kurz A, Sessler DI, for the Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000;342:161-167.
19. Pryor KO, Fahey TJ, Lien CA, Goldstein PA. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population. JAMA 2004;291:79-87.
20. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-1308.
21. Taylor RW, Zimmerman JL, Dellinger RP, et al for the Inhaled Nitric Oxide in ARDS Study Group. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004;291:1603-1609.
22. Spragg RG, Lewis JF, Walmrath H-D, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. N Engl J Med 2004;351:884-892.
23. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2000;(4):CD001744.
24. Stewart AG, Howard P. Indications for long-term oxygen therapy. Respiration 1992;59 Suppl 2:8-13.
25. Gorecka D, Gorzelak K, Sliwinski P, Tobiasz M, Zielinski J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997;52:674-679.
26. Mao C, Wong DT, Slutsky AS, Kavanagh BP. A quantitative assessment of how Canadian intensivists believe they utilize oxygen in the intensive care unit. Crit Care Med 1999;27:2806-2811.
27. Small D, Duha A, Wieskopf B, et al. Uses and misuses of oxygen in hospitalized patients. Am J Med 1992;92:591-595.
28. Jeffrey AA, Ray S, Douglas NJ. Accuracy of inpatient oxygen administration. Thorax 1989;44:1036-1037.
29. Albin RJ, Criner GJ, Thomas S, Abou-Jaoude S. Pattern of non-ICU inpatient supplemental oxygen utilization in a university hospital. Chest 1992;102:1672-1675.

Defining emerging evidence for osmotherapy in traumatic brain injury

Three years ago, an editorial appeared in *Critical Care and Resuscitation* that suggested that "the role of routine osmotherapy remained questionable in neurological emergencies, and that mannitol in particular, should be used with circumspection".[1] Despite

theoretical physiological effects that primarily relate to transient hypervolaemia rather than an osmotic challenge, this negative opinion was based on the narrow therapeutic index of mannitol (particularly when administered to intoxicated patients), the potential to cause hyperosmolarity and diuresis-induced hypovolaemia and hypotension. Furthermore, the paucity of high-level evidence identified by the Brain Trauma Foundation resulted in the recommendation that mannitol be used as an option only in resuscitated patients with unequivocal signs of raised intracranial pressure prior to imaging or evacuation of a mass lesion.[2]

Nevertheless, mannitol remains an established drug in the armamentarium of emergency physicians, anaesthetists, intensivists and, in particular, neurosurgeons.[3] It is often administered in variable doses to patients with a myriad of neurological emergencies, ranging from stroke, hypoxic encephalopathy and traumatic brain injury. Its use is usually justified by anecdotal experience and habit, often with the caveat that in the modern resuscitationist era, hypotension and hypovolaemia are promptly recognised and treated, so that the potential side effects of mannitol are minimised so that the theoretical benefit may exert some effect in patients with life-threatening neurological emergencies.

This latter perception is likely to be encouraged with the recent publication of a study of the effects of "new high-dose" mannitol by Cruz and colleagues.[4] The aim of the study was to target a specific population of severely head-injured patients primarily based on the "presence of recent clinical signs of impending brain death on the first emergency room evaluation." These signs were defined as a Glasgow Coma Score of 3 (or motor score of 1) and bilateral abnormal pupillary dilatation (> 4 mm). Patient selection was further refined to exclude patients with penetrating trauma, systolic hypotension associated with major extracranial trauma and to include only those patients with severe diffuse brain swelling as the predominant intracranial lesion on head CT scan. Over a three-year period, 44 such patients were randomised to receive "ultra-fast intravenous mannitol" in two doses described as "~1.4g/kg and ~0.7g/kg". The doses were based on a 70 kg person, but the actual doses administered were 500 mL ("high dose") and 250 mL ("conventional dose") of 20% mannitol, respectively. During emergency room resuscitation and following admission to the intensive care unit, patients were closely monitored with assiduous attention to oxygenation and haemodynamics. Patients were entered into a "cumulative treatment protocol" that Cruz has previously published, and includes aggressive defence of cerebral perfusion pressure, "optimised" hyperventilation titrated to derived cerebral oxygen extraction ratios, and decompressive craniectomy for refractory intracranial hypertension.[5]

The primary outcome measurement for this study was 6-month dichotomised Glasgow Outcome Score. Not surprisingly, the overall mortality for the patient cohort was high (52%) with 9/23 (39.1%) deaths occurring in the "high dose" mannitol group and 14/21 (66.7%) deaths occurring in the "conventional dose" group. Expressed as dichotomised Glasgow Outcome Score, 10/23 (43%) patients in the "high dose" mannitol group had a favourable outcome compared to 2/21 (9.5%) patients in the "conventional dose" group. This difference achieved statistical significance ($p < 0.02$). Furthermore, Cruz demonstrated that a statistically significant improvement in pupillary diameter occurred in patients who received "high dose" mannitol (14/23; 60%) compared with those who received "conventional dose" mannitol (5/21; 23%). However, there was no difference in the numbers of patients who subsequently developed refractory intracranial hypertension in the intensive care unit (43.5 vs. 47.6%).

The discussion of the results is remarkably long and there is much detail about the justification of neuromonitoring and purported physiological rationale of the relationship between derived cerebral oxygenation measurements and cerebral perfusion pressure. There is no discussion about the statistical design of the study, limitations of sample size or external validity of the results. The study concludes with the statement "…this prospective controlled trial of high dose mannitol…in (patients) with impending brain death, (demonstrated) statistically significant clinical benefits with respect to long term clinical outcomes."

This study received an editorial which acknowledging the provocative nature of Cruz's study, highlighted some limitations.[6] These included concerns about the external validity of the results of this single-centre study (despite the international authorship), and questions about the utility of "optimised hyperventilation" (for which Cruz has been a highly vocal and long-term advocate). The editorial concluded with the comment that a multicentred study should be considered to address the efficacy of "high dose" mannitol. Intriguingly, the journal editor permitted a rapid response letter by Cruz to this editorial in the same issue. Dr Cruz's response is extraordinary and categorically states that, on the basis of his results, "… there is no need for further studies involving our novel high-dose mannitol treatment proposition..." He dismisses any suggestion of inadequacy of power due to close matching of a highly specified study population, and claims that the favourable outcomes he has demonstrated in his patients when compared with historical controls, are primarily a reflection of the quality of overall care that his unit provides.[5]

Whilst it is acknowledged that Cruz went to great

lengths to ensure baseline imbalance and parity of severity of injury to minimise "background noise", there are a number of methodological and interpretative flaws in Cruz's study. Firstly, to confirm the observed reduction in mortality of 27.6% between "high dose" and "conventional dose" mannitol, a sample of 120 patients would be required (80% power, $\alpha = 0.05$). However, accepting that mortality in this patient population is invariably very high and that functional survival is considered to be a more appropriate outcome measure, confirmation of the reduction in unfavourable outcomes from 90.5% to 56.5% would require a sample of 24 patients (80% power, $\alpha = 0.05$). It may be assumed that this is the statistical basis of Cruz's justification for his sample size. However, this is fallacious given the use of composite endpoints such as Glasgow Outcome Score where dramatic changes in one domain may not represent overall changes in the composite score.[7] Secondly, the distinction between "high" and "conventional" dose mannitol is questionable, as the prescribed doses, whilst based on body weight and which Cruz confirms approximated 70 kg in the study population, are such that statistical separation of delivered dose is improbable. Thirdly, it is difficult to attribute such a profound impact on mortality and functional survival by a single intervention. The reliance of "magic bullets" to turn around the devastating pathophysiological process that occur following high-lethality traumatic brain injury is implausible. This has been demonstrated by the inexorable failure of validated neuroprotective agents in improving outcomes in head-injured patients.[7,8] Finally, if such a profound effect were indeed true, then an adequately powered, concealed, randomised trial is required. The feasibility that such trials are possible has been demonstrated by the recent hypertonic saline[9] and saline vs. albumin fluid evaluation (SAFE) studies.[10] Although these two important studies produced "negative" results, they provide clinicians with unequivocal evidence about the efficacy of two fluid resuscitation strategies.

Such an initiative is required for mannitol, before it is accepted as a "proven" therapy. The jury is still very much out on this issue.

Dr. J. A. Myburgh
Department of Intensive Care Medicine
The St George Hospital, Kogarah
NEW SOUTH WALES 2217

REFERENCES

1. Myburgh JA. Osmotherapy in traumatic brain injury - overused and dangerous. Critical Care and Resuscitation. 2001;3:73-74.
2. BTF Guidelines. Brain Trauma Foundation. American Association of Neurological Surgeons. Mannitol. J Neurotrauma. 2000;17:521-526.
3. Myburgh JA, Lewis SB. Mannitol for resuscitation in acute head injury: effects on cerebral perfusion and osmolality. Critical Care and Resuscitation. 2000;2:344-353.
4. Cruz J, Minoja G, Okuchi K, Facco E. Successful use of the new high-dose mannitol treatment in patients with Glasgow Coma Scale scores of 3 and bilateral abnormal pupillary widening: a randomized trial. J Neurosurg. 2004;100:376-383.
5. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. Crit Care Med. 1998;26:344-351.
6. Marshall LF. High-dose mannitol. J Neurosurg. 2004;100:367-368.
7. Maas AI, Steyerberg EW, Murray GD, et al. Why have recent trials of neuroprotective agents in head injury failed to show convincing efficacy? A pragmatic analysis and theoretical considerations. Neurosurgery. 1999;44:1286-1298.
8. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. J Neurotrauma. 2002;19:503-557.
9. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA. 2004;291:1350-1357.
10. The SAFE study investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247-2256.

Where have all the donors gone?

Australia is one of the world leaders in transplantation with excellent survival rates. Liver and heart recipient five-year survival in Australia is 80% and improving.[1,2] However, in Australia, as in all other countries, there are insufficient organs to meet the needs of people with end-stage organ failure who require a transplant. Rates of organ donation in Australia are consistently lower than other Western countries, averaging 9 donors per million population compared with 20 in the United States of America, 19 in France and 12 in the United Kingdom in 2003.[3] Spain has the highest rate of more than 30 donors per million. So why is the rate in Australia comparatively low and is it possible to increase the number of organs available for transplantation?

We have been examining this question since 1997. The potential for cadaveric organ donation in Victoria was estimated in a pilot study undertaken in 1998/1999.[4] This audit aimed to determine the potential for heart-beating (death from brain death) organ donation. All deaths in 12 Victorian hospitals were

reviewed over a 12-month period to identify patients with confirmed or imminent brain death who were medically suitable for organ donation.

This audit estimated the maximal potential donor pool in Victoria to be 30 donors per million. Although a substantial increase from the current rate, this estimate is not practically achievable, as its calculation assumes that all identified patients would proceed to brain death and is based on the family consenting to organ donation all of the time. When these factors are taken into consideration, our realistic maximal rate falls short of the actual rate of organ donation in Spain. Some studies have speculatted that there may be as many as 50 potential donors per million in some communities.[5,6] We clearly have a lower number. Why is there such a disparity?

It is often speculated that the low and falling donation rate in Australia is due to the success of initiatives to lower road trauma, resulting in a smaller donor pool. However, the proportion of donors who arise from individuals dying of trauma in Australia is similar to other countries, so this alone does not explain our lower rate. The audit of hospital records in Victoria provides information about whether missed opportunities for organ donation occur and where efforts might be focused in order to increase the rate of donation. Four possible ways to increase the organ donation rate have been identified.

1. Increasing the consent rate.
2. Increasing the identification of potential organ donors, support to brain death and request for organ donation.

Both of these account equally for the disparity between the maximal potential rate of 30 donors per million and the actual rate of 10 donors per million in Victoria.

3. Ensuring adequate provision of physiological support to brain dead potential donors.
4. Enlarging the potential donor pool with, for example, marginal donors, living donors or non-heart beating organ donors.

We address each in turn.

Increasing the consent rate

In Victoria, non-consent to organ donation by families, as determined by the 1998/1999 pilot study and our ongoing audit, is 40%. There is an increasing political interest in maximising the organ donation rate with the focus being on the consent process and intensive care practice. An Australian Health Ministers Advisory Committee Working Group is currently considering recommendations, which include:

- requiring all clinicians to routinely consult the Australian Organ Donor Register in all brain dead patients to ascertain the deceased's views on organ donation.
- If the deceased has enlisted on the Register, informing the family of the deceased's known wishes after they have been advised that brain death has been confirmed, and advising them that the deceased's known wishes to donate fulfil the requirement for informed consent.
- To not proceed with organ donation if the family raises a sincerely held objection that cannot be reversed by explanation and assurance.

In Australia it is Intensivists who almost exclusively raise the option of organ donation with the family. Intensivists understand the practical issues involved and are best placed to advise on what strategies are feasible and have a moral responsibility to care for the deceased patient's family. We do not support any coercive strategy. Our involvement in the development of any recommendations is critical to the success of their implementation. A survey of families, identified during the 1998/1999 pilot study as having been approached regarding organ donation, found that the family's knowledge of their deceased family member's wishes was the most important factor in influencing their decision whether or not to donate. There was no instance of the family going against the patient's wishes. However, when families did not know their relative's wishes regarding organ donation there was a 50% rate of non-consent. Families also felt burdened in having to make a decision.

As families uncommonly overturn a deceased's wish to donate, focusing on this area may do little to increase the organ donation rate. It is certainly important for the family to take account of the patient's wishes to donate. However, if there is family distress or objection, it is not appropriate to continue with the donation. Proceeding in these circumstances may complicate family members' bereavement and, secondarily, can result in adverse publicity for organ donation if the family make their grievances public.

The importance of individuals informing their family members of their wishes is emphasised in recent organ donation promotions such as the "think, talk, tell - Think about it, Talk about it, Tell your family" campaign. A useful function of the Organ Donor Registry may be to stimulate this type of communication amongst family members.

Family consent rates of up to 80% occur in Spain. This may reflect high societal support of organ donation but may be partly due to the use of repeated requests and persuasive discussions by full-time medical donor coordinators, which would be unacceptable in Australia.[7] Another strategy used in some countries is the adoption of presumed consent legislation. The rationale behind this approach is to promote a culture where organ donation is the norm by changing the default position to one of donation. This removes the

decision-making burden from the family although most countries with such a system still obtain the family's assent prior to proceeding with donation. The attempt to introduce such legislation may be perceived, however, as coercive and impinging on individual freedoms and for these reasons it may not be embraced by the Australian public.

Increasing the identification of potential organ donors, support to brain death and request for organ donation

The second area identified as having an impact on the organ donation rate is the failure, on occasions, to identify potential organ donors or to physiologically support them to brain death and request for organ donation. Auditing of hospital records, in order to identify deceased patients who may have been potential donors, has been undertaken for 2 to 3 years in Victoria, New South Wales, Queensland, Australian Capital Territory and Northern Territory and is about to be implemented in Western Australia. One of the most useful outcomes of the audit has been to confirm, with data, that for greater than 98% of patients with confirmed brain death, organ donation has been discussed with the patient's family. This has enabled us to refute claims that "Intensivists are missing donors".

This ongoing audit review process has the purpose of identifying, and creating a forum for discussion amongst intensivists, a more contentious group of potential donors. These are patients with severe brain injury in whom brain death may have been present, but not formally diagnosed, or in whom brain death has not occurred but is imminent. A typical scenario is the older patient who presents to hospital comatose from a large intracranial bleed and who has a deteriorating neurological state with the absence of some, but not all, brainstem reflexes. Frequently, once the family have been informed of the hopeless prognosis, treatment is withdrawn without informing the family of the possibility of brain death and organ donation. In considering the potential for organ donation, such patients should be viewed as potential donors. Whereas it is the common practice in some hospital emergency departments to withdraw treatment in these patients without referral to intensive care, others routinely admit such patients to the intensive care unit. In the latter scenario it is more likely that brain death will ensue. In addition, in the intensive care unit there are appropriately skilled staff who can raise the possibility of organ donation with the family.

Should all patients with severe brain injury, irrespective of prognosis, be admitted to the intensive care unit? Some Intensivists consider that it is appropriate to admit such patients until the prognosis and response to full supportive therapy is established. The added benefit is the time provided to the family to gather at the bedside, understand the patient's condition and accept the poor prognosis. Other Intensivists consider it unethical to admit patients to the intensive care unit solely for the purpose of facilitating organ donation, unless it is with the family's informed consent and in keeping with the individual's wishes.

Should the option of continuing support in patients who have a hopeless prognosis and the potential to progress to brain death be presented to the family? Who should conduct these discussions? Some Intensivists regularly discuss the option of organ donation prior to brain death confirmation once the family have accepted that their relative's prognosis is hopeless and that they will die.[8] The important principles are to respect the previously expressed wishes of the deceased and the wishes of the grieving family and to fully inform them of the possibility of organ donation. It is essential that such family discussions be conducted with tact and sensitivity by skilled Intensivists to ensure that families do not misunderstand the situation. The various possible outcomes, including failure to progress to brain death in a reasonable time frame, would need to be conveyed. The ability to admit these patients to intensive care units that are already under pressure and under resourced is an important issue.

Ensuring adequate physiological support of the brain dead potential donor

Intensivists perform well in providing adequate physiological support to the potential donor. Less than 5% of consented brain dead potential donors do not proceed to organ procurement because of failed physiological support.[4] This compares well with other reported rates.[9]

Marginal donors, living donors and non-heart beating organ donors

Criteria for donor suitability are constantly being broadened. Marginal donors are older and have more co-morbidities and relative contraindications to organ donation than conventional donors. Factors such as a history of intravenous drug use or cancer are no longer automatic exclusions. Each case should be carefully assessed and the risks weighed against the urgency of transplantation for a potential recipient.

Cautious expansion of criteria, which has occurred with lung donation in Victoria, can result in similar outcomes to conventional donors.[10] Successful kidney and liver transplantations from donors as old as 90 years have been performed in Spain.[11] A recent comparison of donor databases of the United States of America and Spain, however, found a much higher proportion of older donors in Spain but also a higher non-utilisation of procured organs due to organ unsuitability.[12]

Living donation is another source of organs. The

proportion of kidneys transplanted from living donors has increased in Australia, from 24% of all kidneys transplanted in 1996 to 38% in 2002.[13,14] Living donation of liver (partial hepatectomy) and a lung are also possible, although these are associated with a substantial morbidity and mortality risk for the donor. Non-heart beating donation (donation after cardiac death) contributes to very few transplanted organs in Australia (only one donor in 2003).[3] Some centres report that up to 10% of transplanted livers arise from non-heart beating donors.[15] In Japan almost all transplanted kidneys are from non-heart beating donors due to poor public acceptance of recently introduced brain death legislation.[16] Carefully developed protocols are required to guide practice in identifying suitable patients, mode of withdrawal of therapy and timing of declaration of death, managing the logistics of organ retrieval and balancing ethical concerns with the practical issues of minimising warm ischaemia. Non-heart beating donation of lungs has great potential due to a peculiar resilience of the lungs to warm ischaemia, and centres have reported successful results in humans. The feasibility of such a program in Victoria is currently being explored. More important than the logistic concerns are the ethical issues, which are only resolvable by widespread consultation and debate and careful development of safe protocols.

It is clear that the solution to the low organ donation rate in Australia is not simple. The focus of intensivists, however, should not be on increasing the donation rate *per se* but on improving the whole process around potential donation and advocating for the deceased patient and their family. Any valid attempt to increase the rate would require a change in practice that may have resource, clinical and ethical implications. The key role of Intensivists, as the gatekeepers to organ donation, makes it imperative for us to, a) consider whether a patient with a severe brain injury has a potential to progress to brain death and, therefore, be a donor, and b) ensure that we are adequately skilled to talk clearly and compassionately to grieving families about brain death and organ donation.

We wish to thank Professor David Tuxen and Dr. Ray Raper for their helpful comments in preparing this manuscript.

Dr. H. Opdam
Dr. W. Silvester
Intensive Care Unit,
Austin Hospital, Heidelberg
VICTORIA 3084

REFERENCES

1. ANZLT Registry Report 2002. Australia and New Zealand Liver Transplant Registry. Brisbane, QLD, Australia. Editors: S.V. Lynch, G.A. Balderson.
2. National Heart Foundation of Australia: Heart Transplants and Organ Donation. Feb 2004. www.heartfoundation.com.au, accessed 20-8-2004.
3. ANZOD Registry Report 2004. Australia and New Zealand Organ Donation Registry. Adelaide, South Australia. Editors: Lee Excell, G.R. Russ, Penny Wride.
4. Opdam HI, Silvester W. Identifying the potential organ donor: an audit of hospital deaths. Intensive Care Med 2004;30:1390-1397
5. Nathan HM, Jarrell BE, Broznik B, et al. Estimation and characterisation of the potential renal organ donor pool in Pennsylvania. Transplantation 1991;51:142-149.
6. Gortmaker SL, Beasley CL, Brigham LE, et al. Organ donor potential and performance: size and nature of the organ donor shortfall. Crit Care Med 1996;24:432-439.
7. Santiago C. Family and personal consent to donation. Transplantation Proceedings 1997; 29:1625-1628
8. Raper RF, Fisher MM. Brain death and organ donation - a point of view. Anaesth Intensive Care 1995;23:16-19.
9. Navarro A. Brain death epidemiology: The Madrid study. Transplant Proc 1996;28:103-104.
10. Gabbay E, Williams TJ, Griffiths AP, et al. Maximizing the utilization of donor organs offered for lung transplantation. Am J Respir Crit Care Med 1999;160:265-271.
11. Lopez-Navidad A, Caballero F. For a rational approach to the critical points of the cadaveric donation process. Transplant Proc 2001;33:795-805.
12. Chang GJ, Mahanty HD, N.L. A, et al. Expanding the Donor Pool: Can the Spanish Model Work in the United States? Am J Transplant 2003;3:1259-1263.
13. ANZDATA Registry Report 1997. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia. Editors: A.P.S Disney, G.R. Russ, R. Walker, A.G.R. Sheil.
14. ANZDATA Registry Report 2003. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia. Editors: Stephen McDonald and Graeme Russ.
15. Reich DJ, Munoz SJ, Rothstein KD, et al. Controlled non-heart-beating donor liver transplantation: a successful single center experience, with topic update. Transplantation 2000;70:1159-1166.
16. Hattori R, Ono Y, Yoshimura N, et al. Long-term outcome of kidney transplant using non-heart-beating donor: multicenter analysis of factors affecting graft survival. Clinical Transplantation 2003;17:518.