

# The pupillary light reflex in the critically ill patient

The pupillary response to light is controlled by the autonomic nervous system. The direct pupillary light reflex refers to miosis that occurs in the stimulated eye; the consensual pupillary light reflex refers to miosis that occurs in the other eye. The reflex has a latent period with length of the period, amplitude of the response, and the speed of the pupillary constriction dependent on the intensity of the stimulus employed.<sup>1</sup> For the reflex to be truly tested, an intense stimulus and close observation are required. The reflex has afferent, efferent and central connections; therefore non-response to light (i.e. reflex iridoplegia) indicates a disturbance in one or all of these connections.

As areas in the brainstem controlling consciousness are anatomically adjacent to the autonomic fibres controlling the pupillary responses, the pupillary light reflex is a valuable guide to the presence and location of brainstem diseases causing coma. Moreover, because the pupillary response is relatively resistant to metabolic insult, the presence or absence of the light reflex is often used as the single and most important physical sign to distinguish a structural (i.e. potentially irreversible) from a metabolic (i.e. reversible) cause of coma. With brainstem destruction the pupillary reflex is lost whereas the size of the pupil may change (albeit slowly),<sup>2</sup> thus the 'fixed' element is more important than the 'dilated' element in the clinical sign of 'fixed dilated pupils'

Although interobserver agreement on the presence or absence of the light reflex is one of the most consistent measures of brain-stem function, approximately 30% disagreement exists regarding the status of this reflex in comatose patients.<sup>3,4,5</sup> The interobserver disagreement arises partially from the lack of a standard method to elicit the reflex. Traditionally the pupillary light reflex is determined using a penlight (i.e. pencil torch) and factors such as the amount of ambient light in the room, the observer's visual acuity, the distance of the penlight bulb from the patient's pupil and strength of the penlight batteries can alter the validity of the visual assessment of the reflex. The reflex is also more difficult to detect with a wide pupil (e.g. a 0.2 mm reflex in a 5 mm diameter pupil is only a 4% reflex, whereas the same reflex in a 2 mm diameter pupil is a 10% reflex) and in a dark iris (as the ambient

light must be high for the iris to be seen, which reduces the step increase induced by the penlight).<sup>6</sup>

If the pupillary light reflex amplitude is less than 0.3 mm and the maximum constriction velocity is less than 1 mm/s, the reflex is unable to be detected using a penlight.<sup>6</sup> In conscious patients with Holmes-Adie and Argyll-Robertson pupils with 'absent' pupillary light reflexes, small light reflexes have been detected using infrared pupillometry.<sup>7</sup> Also in post-resuscitation non-brain dead critically ill patients with 'absent' pupillary reflexes, the reflex has been demonstrated using a portable infrared pupillometer.<sup>6</sup>

In this issue of *Critical Care and Resuscitation*, Thomas<sup>8</sup> describes a case of Guillain Barré syndrome presenting with weakness and fixed dilated pupils who subsequently became 'locked in' with absence of any clinical response to external stimuli. A positive brain stem auditory evoked response was used to indicate normal brain stem function. In another recent report, a case of 'reversible fixed dilated pupils' was associated with carbamazepine and venlafaxine overdose.<sup>9</sup> Both reports highlight the importance of the reflex and together probably give the reader a complete list of the common and rare causes of 'fixed dilated pupils'. However, from recent reports it would appear that some of these conditions might be associated with 'clinically undetectable' rather than 'absent' pupillary light reflexes.

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## Haemodynamic targets in shock: choosing a pressure

In his comprehensive review of shock, Worthley<sup>1</sup> reminds us that despite the knowledge explosion regarding its possible mediators, this has not yet translated into clinically useful therapeutic interventions. Consequently, haemodynamic resuscitation remains central to management. While it is clear that many manifestations of shock are not simply due to the effects of inadequate nutritional blood flow ( $\dot{Q}$ ), this is often a precipitating and compounding factor leading to organ dysfunction and death. However, optimization and augmentation of regional  $\dot{Q}$  remains polemic, often resulting in arguments surrounding adequacy of perfusion pressure, systemic  $\dot{Q}$ , and specific regional vascular effects of drugs. Regional  $\dot{Q}$  is determined by the inflow pressure ( $P_i$ ), the outflow pressure ( $P_o$ ), and the regional conductance ( $c$ ):

$$\dot{Q} = (P_i - P_o) \times c$$

and while  $P_o$  is often neglected or simply thought of as the regional venous pressure,  $\dot{Q}$  ceases at a  $P_i$  well above the venous pressure (often 30 - 40 mmHg). This is termed the critical closing pressure of that organ, and reflects both tissue pressure (which in turn will be influenced by venous pressure) and the smooth muscle tone of terminal arterioles and precapillary sphincters. In organs such as the brain and kidney, with tight pressure-flow autoregulation,  $\dot{Q}$  falls once pressure is reduced below their autoregulatory threshold. Pressure reductions prior to that are compensated by a rise in regional conductance, however, when the regional vasodilator reserve is reached, flow falls linearly with pressure.

In healthy subjects the autoregulatory threshold for the brain is ~85 mmHg; however this represents the mean from a wide range (~50 - 100 mmHg), and patients with treated hypertension have a right shifted curve with their mean autoregulatory threshold ~110 mmHg.<sup>2,3</sup> Although these data may seem high, similar estimates have been published for the renal autoregulatory threshold.<sup>4,5,6</sup> In acute renal failure,<sup>7,8</sup>

models of meningitis<sup>9</sup> and some patients with traumatic brain injury, pressure flow-autoregulation is markedly impaired with no ability to defend  $\dot{Q}$  in face of changing  $P_i$ . Using endotoxin as a model of sepsis, there also appears to be a left shift of the renal autoregulation curve.<sup>10,11</sup> Although this results in an elevated  $\dot{Q}$  at a given  $P_i$ , when this falls the steeper pressure-flow curve results in greater falls in renal  $\dot{Q}$ . Taken together, these data suggest that from the perspective of these organs, blood pressure must be defended to at least a mean of 80 mmHg. While differences in outcome have not been demonstrated, this is supported both by studies demonstrating increases in  $\dot{Q}$  with vasopressors such as noradrenaline or adrenaline, and by many anecdotal series. However, since there is a range of autoregulatory thresholds in the normal population 80 mmHg may be higher than necessary in some patients, but insufficient in others. Finally, since high doses of these agents may right shift the pressure-flow curve demanding a higher blood pressure to maintain  $\dot{Q}$ , these drugs must be carefully titrated.

It is also important to consider metabolically active tissues such as muscle which also depend upon pressure to maintain  $\dot{Q}$  when vasodilator reserve is no longer available. For example, in the ischaemic dog heart Braunwald and coworkers<sup>12</sup> found that isoprenaline, dobutamine and nitroglycerine infusions resulted in a worsening of ischaemia and function because changes in myocardial work were not matched with changes in coronary perfusion pressure. However, noradrenaline infusion improved myocardial contractility without worsening ischaemia since perfusion pressure increased. These data mimic that reported in patients with cardiogenic shock,<sup>13</sup> and while intra-aortic balloon counterpulsation achieves an increase in perfusion pressure with a reduction in work, this may not be appropriate in all patients. Similar data, emphasizing the importance of perfusion pressure through its defense with vasopressors resulting in improved function, have been reported both for the right ventricle<sup>14,15</sup> during pulmonary hypertension, and the diaphragm during inspiration.<sup>16,17</sup>

Where then does this leave the clinician? Much of this data is from animal models or utilizes techniques not commonly available at the bedside. Properly controlled trials looking at a target blood pressure have not been performed and are unlikely to be at a high priority. However, there does seem to be a reasonable body of data supporting a target mean blood pressure significantly greater than 60 mmHg.<sup>1</sup> This may require the use of vasopressor catecholamines, but with the proviso that their use is titrated to clinical effect and that systemic flow is adequate, the risk:benefit ratio favours a consequent increase in regional  $\dot{Q}$ .

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## The ANZICS clinical trials group

There has been a growing perception that a powerful way to advance the quality of practice in Critical Care Medicine is through the increasing application of the concepts of Evidence Based Medicine (EBM).<sup>1</sup> However, intensive care units (ICUs) have a limited throughput of patients (typically no more than 2000/year) and an extraordinarily heterogeneous patient population. Furthermore, such patients undergo a myriad of interventions every day and the effects of therapeutic maneuvers on patient outcome are difficult to discern, except for extreme situations.

The combination of confounding variables, limited numbers, patient heterogeneity, urgency of treatment and heuristic bias pose serious obstacles to the gathering of high-quality evidence upon which to base our clinical practice.<sup>2</sup>

One possible response to such significant logistic difficulties would be to accept defeat and to continue to practice on the basis of physiological reasoning, experience, mentorship, local folklore and personal bias. Many Australasian intensivists, however, feel uncomfortable with such defeatist attitudes and believe that much can be achieved if resources are pooled and a commitment is made to the process of gathering evidence through randomised controlled studies. These clinicians have progressively gathered momentum and organisational strength over the last five years and are now steadily making progress under the banner of the ANZICS Clinical Trials Group (CTG). This group, which first met in 1994 in Sydney, has published its first epidemiological study<sup>3</sup> and has recently completed its first double-blind randomised controlled trial. This trial compared low-dose dopamine with placebo for renal rescue in patients with early renal dysfunction and involved 328 patients in 23 units. It has just been submitted for publication.

As the CTG has progressed in its efforts, it has also grown in membership and organisation. It held its first separate meeting in Noosa in 1999 and will be holding its second yearly meeting in Surfers Paradise on April 15 and 16, 2000. It now has a web site (<http://anzics.herston.uq.edu.au/zindex.html>) and an executive. Membership remains open to all interested physicians and nurses.

The growth in membership and organisation has come hand in hand with an increase in its activities and in the scope of its goals. A large multicentre epidemiological study of the incidence and outcome of sepsis in Australian and New Zealand ICUs has just been completed and data entry is under way. To our knowledge, this is the largest prospective study of this kind in the world. Similarly, another epidemiological study of the incidence, treatment and outcome of acute lung injury/acute respiratory distress syndrome (ALI/ARDS or the ALive study) has just been completed in 3 Australian States involving all such patients over a predetermined time period. Preliminary data will be presented in April 2000. April 2000 is also the starting time for the Traumatic Brain Injury epidemiology study, another ambitious project that, together with the sepsis and ALI studies will allow us to plan future interventional trials. Finally, an enormous organisational effort is now under way involving 90 clinicians, 13 large ICUs and the Institute for International Health. This effort is aimed at conducting the largest randomised, double-blind controlled ICU study so far, a study which will test the efficacy and safety of resuscitation with 4% albumin.

The growth of the CTG has also gone hand in hand with the growth of the ICU Foundation. The two organisations, with the continuing support and encouragement of the ANZICS Board, have developed a symbiotic relationship in which fund raising, trial design, goal setting and strategy development have become a continuing process.

I believe there has never been a more exciting time for those who can see the advantages of EBM and the extraordinary benefits of collaborative work. Indeed, it is possible that, because of these efforts, in the next 5 years, Australia and New Zealand will be seen as a model of how to advance the science and practice of Critical Care Medicine.

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## Microwave warming of fluids - pH and other questions

In this issue of *Critical Care and Resuscitation*, Drs Steele and Story investigate whether microwave heating of 0.9% saline packaged in standard polyvinyl chloride (PVC) bags changes pH.<sup>1</sup> They heated 1 litre and 100 mL bags to unspecified temperatures in an 800 watt oven on the 'high' setting for 2 minutes and 30 seconds respectively and found that the pH of the saline measured the next day at ambient temperature was the same as that of unheated controls. However there was a statistically significant difference in pH between the 1 litre bag specimens (pH ~ 5.0 for both heated and control bags) and the 100 mL specimens (pH ~ 4.6). Although it was not possible to incriminate microwave heating, the authors speculate that this pH discrepancy might have been caused by acids released from the PVC packaging in differing amounts due to the different surface area to volume ratios of the 1 litre and 100 mL bags. They suggest that such products of PVC degradation might include the plasticiser di(2-ethylhexyl) phthalate (DEHP), as well as formic and acetic acids. However, none of these compounds were assayed in their experiment.

Are these valid suggestions? The finding of an acid pH is no surprise in itself, despite the fact that NaCl solutions in pure water have a neutral pH. Many crystalloids prepared commercially for infusion are known to have an acidic pH. For example, in one study the pH of four different 0.9% saline preparations ranged from 5.35 – 5.95, and the pH of four 5% dextrose preparations was even lower (4.2 – 4.85).<sup>2</sup> The acidity of dextrose solutions has been variously attributed to dissolved atmospheric CO<sub>2</sub>,<sup>3</sup> the production of small amounts of sugar acids,<sup>3</sup> inherent acidity,<sup>4</sup> caramelisation during autoclaving,<sup>5</sup> pH adjustment by the manufacturer in order to prevent caramelisation,<sup>6</sup> or pH adjustment by the manufacturer to facilitate sterilisation and otherwise improve the stability of dextrose preparations.<sup>7</sup> Dissolved atmospheric CO<sub>2</sub> is also the usual explanation proffered for the acidity of saline preparations.<sup>3</sup>

For years the causes and significance of the low pH of crystalloid fluids has been a confusing topic, hence beloved of College examiners in basic science. What is commonly overlooked is that the titratable acidity of these crystalloids is minuscule. For example, the titratable acidity of the aforementioned 0.9% saline preparations (defined as the concentration of titratable hydrogen ion required to bring the pH to 7.4) ranged

from 0.126 - 0.152 mEq/L.<sup>2</sup> This is so low that when 0.9% saline is added to blood *in vitro* at pH = 7.4, there is only a very slight pH reduction. The rule holds true even with significant dilutions (e.g. 1:1 vol:vol) because of the large buffering capacity of blood, provided there is no change in haemoglobin-oxygen saturation - a fact alluded to previously in this journal.<sup>8</sup> The acidity of crystalloid fluids such as saline will thus not cause local venous damage on infusion. Nonetheless, significant metabolic acidosis can still result from the *in vivo* infusion of 0.9% saline.<sup>9</sup> This has nothing to do with the intrinsic pH of the infusion fluid and everything to do with alteration of the pCO<sub>2</sub>/pH relationship as a consequence of altered buffer base concentration (strong ion difference).<sup>10</sup>

Drs Steele and Story have now added another tentative explanation for these small amounts of titratable acid in commercial preparations of normal saline - that of acid release by the PVC packaging. They advance this possibility on fairly tenuous evidence - the demonstration of differences in the pH of 100 mL and 1 litre bags which are unaffected by microwave heating. The most obvious deficiency with this reasoning is that they have not yet proved that saline in 100 mL bags is always more acidic than saline in 1 litre bags. Many batch numbers need to be tested to confirm it is a bag volume specific rather than a batch specific phenomenon. Bags from different manufacturers also need evaluation. Even if the phenomenon is found to be consistent, PVC packaging seems an unlikely culprit. The fact that the pH range of 5% dextrose quoted by one manufacturer is the same whether it is packaged in glass or PVC (pH = 3.5 - 6.5, Baxter, Australia) certainly fails to support the proposition. The authors' conclusion that 'no further acids are released' as a result of microwave heating would be better stated simply as 'no acids are released'.

Is this interest in microwave heating of fluids relevant to critical care practice? Do microwaves have special properties of use to intensivists? Microwave energy is a form of non-ionising electromagnetic radiation, with a frequency of 300 MHz to  $3 \times 10^6$  MHz - between radiofrequency and infrared in the electromagnetic spectrum.<sup>11</sup> When substances are traversed by microwave radiation, warming occurs by production of molecular vibration in dipoles. Liquid water is therefore an ideal medium for microwave heating.<sup>12</sup> Substances with low dielectric properties such as plastics and ceramics do not absorb energy from microwaves, and will undergo a temperature increase by conduction from contained fluids. Similarly, ice absorbs microwaves poorly, and is thawed during microwave irradiation mainly by contact with adjacent heated water.<sup>13</sup>

Medical applications of microwave technology

include thermal coagulation,<sup>11</sup> enhancement of chemotherapy and other oncological treatments,<sup>14-17</sup> and in histopathology.<sup>18</sup> The application stimulating the interest of Drs Steele and Story is the use of microwave technology in warming fluids for intravenous administration and lavage.<sup>19</sup> This has additional relevance to an article on accidental or therapeutic hypothermia also in the current issue.<sup>20</sup> Here Drs Connolly and Worthley reveal that peritoneal lavage with dialysate at 44°C during the attempted reversal of hypothermia transfers heat as efficiently as extracorporeal techniques. Although heating intravenous fluids to 41°C makes only a relatively small contribution to rewarming, efficient and accurate warming of resuscitation fluids during large volume resuscitation, such as in burns or major trauma is important to prevent heat loss. Which leads us to ask whether anything is to be gained from employing microwave technology as a means of heating fluids for resuscitation and lavage. What are its advantages and disadvantages compared with the more conventional devices such as incubators, waterbaths, thermal jackets and countercurrent heat exchange units?

Firstly, the question of plasticiser toxicity raised by Drs Steele and Story needs to be dealt with. DEHP is in common use as a plasticiser in the PVC of commercial IV bags and lines. It is known to leach into intravenous fluids, particularly during high intensity blood - PVC interactions such as extracorporeal circuits.<sup>21,22</sup> Although many potential toxic effects have been ascribed to DEHP and its metabolite mono(2-ethylhexyl) phthalate (MEHP), including lipid peroxidation of stored erythrocytes,<sup>23</sup> cardiotoxicity,<sup>24</sup> hepatotoxicity<sup>25</sup> and pulmonary toxicity,<sup>26</sup> the jury is still out on whether plasticiser leaching is a genuine problem in normal clinical scenarios.<sup>22</sup> What does seem definite is that microwave heating of PVC packaged fluids does not increase the risk of DEHP exposure compared with other heating techniques.<sup>13, 27,28</sup> There is also no clear evidence that microwaves cause direct tissue damage in the absence of a significant temperature rise. No particular antimicrobial propensity has been identified beyond that of heating.<sup>29</sup>

The main advantage of microwave heating is speed. For example, 1 litre bags of crystalloid at 21°C can be heated to 32°C, 45°C and 53°C in 2, 4 and 5 minutes respectively.<sup>30</sup> Units of fresh frozen plasma can be thawed in a microwave oven in 5 to 8 minutes, as compared with 20 to 30 minutes in a 37°C circulating water bath.<sup>13</sup> Potential benefits arising from this kind of heating efficiency during urgent intravenous resuscitation are self-evident. However, there is a downside. There are no universally applicable heating formulae, and ovens need individual calibration. It is also wise to check the temperature of all fluids before

infusion, as thermal injury at a peripheral infusion site has been reported.<sup>31</sup> It is usual to restrict the temperature of infused fluids to 41°C to avoid haemolysis, especially during peripheral administration.

Another problem is the uneven nature of the heat exchange process, with the creation of 'hot spots'. In the case of fresh frozen plasma, precipitation of plasma proteins and loss of coagulation factors can result, even when short pulses of irradiation are interspersed with pauses to allow redistribution of heat.<sup>13</sup> Blood units can develop gross haemolysis in areas of local overheating,<sup>32</sup> and at least one fatality connected with this phenomenon has been reported.<sup>33</sup> The 'hot spot' problem can be reduced if bags are rotated or agitated during irradiation. Shielding of spike ports and the tapered ends of IV bags is also useful. In a purpose-made device with the further modifications of a temperature sensor and automatic shut-off at 21°C, safe and rapid thawing of frozen plasma without significant loss of coagulant activity has been demonstrated.<sup>34,35</sup> However, many hospital blood banks still use circulating water baths in preference to purpose-made microwave devices to thaw frozen plasma, mainly to save money.

Finally there has been a significant development in the rapid heating of red cell preparations for intravenous infusion – the in-line microwave blood warmer.<sup>36-38</sup> In an *in vitro* study a group from Boston has shown the heating performance of in-line microwave blood warming devices to be better at high flow rates (exceeding 500 mL/minute) than that of state of the art single channel countercurrent heat-exchangers.<sup>37</sup> Indices of haemolysis did not increase with either type of warming device at this flow rate. Because lower flow rates are associated with longer in-line exposure times, there is an increased haemolysis potential. However, here again haemolysis was minimal and not worse than that associated with the conventional heat-exchanger. The same research group has now published evidence that blood heated to temperatures as high as 49°C remains haemolysis-free using these in-line devices.<sup>38</sup> Clinical evaluation is awaited with interest. Apart from a need for recalibration, there would appear to be no reason why the technology could not be extended to the warming of rapidly infused crystalloids.

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