Point of view

The case for a standardised protocol that includes hormone resuscitation for the management of the cadaveric multi-organ donor

The success of organ transplantation is critically dependent on the quality of the donor organ. Donor organ quality in turn is determined by a variety of factors including donor age and pre-existing disease, the mechanism of brain death, donor management prior to organ procurement, the duration of hypothermic storage and the circumstances of reperfusion. As demand for solid organ transplantation has increased so has the use of “marginal” donors (e.g. those obtained from older donors or from donors with evidence of chronic organ disease or dysfunction prior to brain death). Thus, many cadaveric organs offered for transplantation have pre-existing disease or dysfunction prior to the onset of brain death. Although results obtained with marginal donors are generally regarded as acceptable (at least in relation to the waiting list mortality), it is clear that both short-term and long-term post-transplant outcomes are not as good when compared with organs obtained from “conventional” donors.2,3 Furthermore, while the use of marginal donors has led to an increase in the potential donor pool, it has also led to an increased discard rate of cadaveric organs offered for transplantation. For example, as reported by Rosendale et al,1 “the discard rate of kidneys procured from the cadaver donor in United States of America has been increasing to an alarming level of more than 15% of those kidneys recovered for transplantation”. The discard rate for other organs is even higher. Approximately 25% of livers and 60% of hearts and lungs from cadaveric donors are not transplanted due to poor donor organ quality.4,5

Another factor that adversely affects donor organ quality is brain death. It has been recognised for some time that both the short-term and long-term outcomes after cadaveric organ transplantation are significantly inferior to those obtained when the transplanted organ is obtained from a living donor, regardless of whether the donor is related or unrelated to the recipient.6 Brain death results in a series of haemodynamic, neurohormonal and pro-inflammatory perturbations all of which are thought to contribute to donor organ dysfunction.

Finally, the process of transplantation exposes the donor organ to an obligatory period of ischaemia and reperfusion. Traditionally, hypothermic storage of the donor organ has been used to protect it from ischaemic injury, however, donor organs differ markedly in their capacity to withstand hypothermic ischaemia. In this review, strategies aimed at minimising the adverse consequences of brain death on donor organ quality will be discussed. We believe that these strategies will become increasingly important as the reliance on marginal donors increases to meet the growing demand for organ transplantation.

The haemodynamic, neurohumoral and immunological consequences of brain death

*Haemodynamic changes: Brain death is accompanied by a series of complex haemodynamic, neurohormonal and immunological changes. The time course and severity of these changes may vary according to the tempo and the nature of the neurological insult leading to brain death. The most severe changes are usually seen in the setting of acute onset of brain death (such as occurs with severe intracranial haemorrhage), which is associated typically with an acute and intense autonomic discharge, characterised by initial bradycardia (parasympathetic discharge) followed by extreme tachycardia and hypertension (sympathetic discharge). Potential donor organs suffer an ischaemic insult during this phase, the heart due to a massive increase in workload7 and the peripheral organs due to intense peripheral vasoconstriction.8 This autonomic storm has its onset within the first few minutes and has usually passed within 15 minutes. The autonomic storm is also characterised by a sudden increase in cytosolic calcium, which in turn activates enzymes such as lipase, protease, endonuclease, nitric oxide synthase and xanthine oxidase.9 These enzymatic changes disrupt normal ATP utilisation and generate oxygen free radicals, which contribute to organ failure. Thereafter, there is a loss of sympathetic tone associated with persistent tachycardia and hypotension. The loss of autonomic tone also results in impaired vascular autoregulation with diminished blood supply and oxygen delivery to organs and tissues. Both initial and late circulatory changes can lead to severe ischaemic damage in donor organs before their removal, causing deterioration of the quality of the transplanted graft.

*Neurohormonal changes: Although most investigators accept a link between brain death and disruption of the hypothalamic-pituitary axis, there are conflicting data regarding the hormonal changes that occur during and after central nervous system injury and their influence on haemodynamic parameters and organ quality.9-11 In animal models, the hormonal changes fall into two categories: those associated with the autonomic
storm represent a transient and massive increase in circulating catecholamines, and those associated with hypothalamic-pituitary failure lead to neurogenic diabetes insipidus and a marked decrease in levels of thyroid hormones and cortisol, at least in animal models.\textsuperscript{12,13} Metabolic abnormalities associated with these hormonal perturbations include impaired aerobic metabolism despite normal O\textsubscript{2} delivery. This has been demonstrated both globally,\textsuperscript{14} and in specific organs including the heart\textsuperscript{15} and kidney.\textsuperscript{15} The consequent reliance on anaerobic metabolism results in lactic acidosis\textsuperscript{12,14,15} and rapid depletion of high-energy substrates such as ATP.\textsuperscript{15} Progressive depletion of high-energy stores has been reversed successfully by a combination of tri-iodothyronine (T\textsubscript{3}), cortisol, and insulin administration, suggesting that hormonal changes are the major cause of mitochondrial dysfunction with impaired energy production at the cellular level.\textsuperscript{16}

Some investigators, however, have demonstrated only minor hormonal changes in humans after the onset of brain death.\textsuperscript{17,18} An extensive survey of studies on brain-dead human donors indicates that a reduction in the level of free T\textsubscript{3} has almost always been documented, but changes in other hormone levels (such as TSH, T\textsubscript{4}, and cortisol) are variable.\textsuperscript{17-21} Levels of reverse T\textsubscript{3} have been found to be normal or increased after brain death consistent with a “sick euthyroid” state. Differences between experimental and some clinical findings may be explained by the fact that the former are determined with a uniform mechanism of brain death in highly controlled systems in contrast to the latter group, in which patients suffer brain death by a variety of mechanisms.

**Immunological/inflammatory changes:** Studies investigating the relation between brain death and immunological activation of peripheral organs have demonstrated that the explosive increase in intracranial pressure followed by systemic hypotension, up-regulates various lymphocyte-and macrophage-derived cytokines on solid organs in rats.\textsuperscript{22} The hypothesis that brain death increases the immunogenicity of solid organs is further supported by findings that kidneys and hearts transplanted from brain-dead donor animals experience accelerated acute rejection compared to those from living donors.\textsuperscript{23} Early adhesion molecules (selectins) not present on the vascular cell surface under resting conditions but up-regulated rapidly after injury, seem to trigger subsequent events. Adherent leukocyte populations express other classes of adhesion molecules (intercellular adhesion molecule; vascular cell adhesion molecule; lymphocyte-function associated antigen-1) and release proinflammatory lymphokines (TNF\textalpha, interferon-\gamma). Expression of major histocompatibility complex (MHC) class I and II molecules is increased. The up-regulation of MHC on graft cells is mediated primarily by interferon-\gamma, itself increased by the brain death/ischemia/reperfusion insult. The mediators of immunological activation of donor organs after brain death have not been determined. The deleterious changes in endothelial surfaces and the increasing immunogenicity of solid organs begin promptly after massive central injury and it has been suggested that these changes can be partly explained by excessive catecholamine release.\textsuperscript{3} This hypothesis is further supported by the experimental observation that even short-term administration of catecholamines in brain-dead donors is followed by reduced survival and poor initial function after renal allotransplantation in pigs.\textsuperscript{24}

**Intensive care unit management of the brain-dead organ donor**

Donor management has been described as “the most neglected area of transplant medicine.”\textsuperscript{25} In one study, it was estimated that failure to provide adequate physiological support to potential donors accounted for at least 25% of lost donor organs.\textsuperscript{26} Data from the Australia and New Zealand organ donation (ANZOD) registry\textsuperscript{27} reveals that more than 90% of brain dead individuals develop hypotension and receive some form of inotropic/pressor support, most commonly noradrenaline. Other inotropic/pressor agents used include adrenaline, dopamine, dobutamine and metaraminol. The choice of agent is likely to reflect local preferences, but currently there is little evidence to support the use of any single catecholamine over others. The duration of pressor support varies considerably, but 90% of brain dead donors receive support for between 6 and 24 hours, prior to donor organ removal.

The impact of the administration of catecholamines to the brain-dead donor on subsequent graft outcome remains unclear. Experimental studies in solid organ transplantation and clinical studies in heart transplantation have generally demonstrated worse outcomes when the donor has received catecholamines.\textsuperscript{24,28-32} On the other hand, several clinical studies, including a recent meta-analysis, found that that graft outcomes after kidney transplantation were better when donor kidneys were obtained from donors who had received catecholamines.\textsuperscript{32} In this same meta-analysis, heart transplant outcomes were worse and liver transplant outcomes were unaffected by donor catecholamine treatment. At present, it is unknown whether these differences in transplanted organ outcomes reflect differences in the type of donors that receive catecholamines, the direct effects of catecholamines on different donor organs or indirect effects (such as better maintenance of blood flow to the kidney in donors receiving catecholamine infusions). Regardless of the explanation, this observation creates an immediate
dilemma for the intensive care physician caring for the brain dead donor. Does he/she administer a drug which appears to benefit one potential donor organ but harms another?

A series of observations reported by Rosendale et al., suggests that it may not be necessary to optimise preservation of one organ at the expense of another. In a large retrospective review of the organ procurement and transplantation network (OPTN) database, they noted that 15% more kidneys were transplanted from donors whose heart was transplanted: 91% vs 76% (p < 0.001). Furthermore, kidneys from heart donors had a lower incidence of delayed graft function: 18% vs 25% (p < 0.001) and better one year survival: 91% vs 87% (p < 0.001). These data suggest that donor treatments that optimise the function of the donor heart (and cardiac output) are likely to benefit donor kidney function as well (and presumably the function of other donor organs).

Hormonal resuscitation of the brain dead donor

Generally accepted principles of donor management include correction of any fluid imbalance by intravenous fluid replacement, treatment of diabetes insipidus, maintenance of blood pressure using vasoconstrictors (usually) or vasodilators, with maintenance of adequate ventilation and electrolyte homeostasis. However, there is no consensus regarding correction of hormonal abnormalities in the brain dead donor other than treatment of diabetes insipidus. Even the use of vasopressin or its synthetic analogue desmopressin is contentious as both have been reported to impair perfusion of the donor pancreas. On the other hand, there is a paucity of data on the effects of other vasopressor agents on perfusion of the donor pancreas or other intra-abdominal organs.

Almost 50 years ago, Wagner and Braunwald demonstrated that patients with autonomic failure were exquisitely sensitive to the vasoconstrictor effects of vasopressin, whereas minimal vasopressor effects were demonstrable in normal subjects. In 1986, Yoshioka and colleagues demonstrated that brain-dead subjects could be maintained in a stable haemodynamic state for an average of 23 days using a combination of low-dose vasopressin and adrenaline. In the same study, brain dead subjects treated with adrenaline alone all progressed to cardiac arrest at an average of 24 hours after brain death. More recently, several investigators have demonstrated that low-dose vasopressin is effective in restoring blood pressure and systemic vascular resistance in haemodynamically unstable brain-dead donors. Low-dose vasopressin has been shown to be effective in maintaining hepatic energy metabolism after brain death in experimental dogs. Furthermore, human studies have shown that renal and hepatic function are well preserved in brain-dead patients supported with low-dose vasopressin infusions.

Clinical trials of thyroid hormone administration to the brain dead donor have shown variable efficacy. There are several possible explanations for the discordant results observed in clinical trials to date. In general, studies in which the brain-dead donor has been treated with thyroid hormone alone (either T3 or T4) have failed to demonstrate any haemodynamic benefit associated with this treatment. In contrast, studies of hormonal replacement in which thyroid hormone has been administered in combination with cortisol or as part of a multi-hormone “cocktail” have demonstrated favourable effects on donor haemo-dynamic status. The extent of hormonal disturbance and the impact this has on donor organ quality may vary among donors, depending on the clinical circumstances leading to brain death. Retrospective analysis of these studies suggests that combined hormonal therapy is most useful in haemodynamically unstable donors, those with impaired left ventricular function on echo-cardiography or those requiring prolonged vasopressor support.

Perhaps the most supportive clinical study for combined hormonal therapy was that performed by Wheelerd and colleagues. Based on the experimental work of Novitzky and colleagues, they developed a combined infusion of triiodothyronine, methylprednisolone, vasopressin and insulin, which has subsequently become known as the “Papworth cocktail”. They reported that in 150 consecutive multi-organ donors, 52 hearts were “unacceptable” for transplantation based on conventional selection criteria. Forty four of these 52 “unacceptable” hearts (92%) became acceptable after institution of Swan-Ganz monitoring, haemodynamic “optimisation” and administration of combined hormonal therapy. Importantly, similar post-transplant outcomes were observed after transplantation of these resuscitated hearts compared with organs that initially met “acceptable” criteria. Largely based on the results of this study, a recent consensus meeting of various stakeholders in the United States of America developed a uniform cadaveric donor management protocol (Figure 1) that incorporates invasive haemodynamic monitoring and hormonal resuscitation (HR) for donors that are haemodynamically unstable.

Recently, Rosendale et al., published the findings of a large retrospective analysis of all brain-dead donors recovered in the United States from January 1, 2000, to September 30, 2001. Of 10,292 consecutive brain-dead donors analysed, 701 (7%) received three-drug HR (triiodothyronine or L-thyroxine, methylprednisolone and vasopressin). Univariate analysis showed the mean number of organs from HR donors (3.8) was 22.5% greater than that from non-HR resuscitation donors (3.1) (P < 0.001). Multivariate analyses showed that HR was...
**Conventional Management**
- Adjust volume status: target CVP = 6-12 mmHg
- Adjust noradrenaline to keep MAP ≥ 60 mmHg (target noradrenaline dose ≤ 0.2 μg/kg/min)
- Correct acidosis: target pH = 7.35-7.45
- Correct hypoxaemia: target pO₂ > 80 mmHg, O₂ sat. > 95%
- Correct blood glucose: Insulin: 1 Unit/hr titrate to BGL 6-10 mmol/l

**Obtain initial Echo**
- Rule out structural abnormalities (substantial LVH, valvular disease, congenital lesions)

**Normal Echo and Stable haemodynamics**

**Abnormal Echo* and/or Unstable haemodynamics#**

**Hormonal Resuscitation (HR)**
- Methylprednisolone: 15 mg/kg IV bolus
- Start Vasopressin: infusion 2.4 Units/hr
- T3: 4 μg IV bolus + infusion 4 μg/hr

**Ongoing Haemodynamic Management**
Adjust fluids and noradrenaline infusion rate at 15 min intervals to minimise use of noradrenaline and meet the following **target criteria**:
- MAP > 60 mmHg
- CVP = 6-12 mmHg
- Noradrenaline ≤ 0.2 μg/kg/min

**Criteria Met**
- Recover Heart

**Criteria Not Met**
- Discuss with Heart Transplant Team regarding recovery of the heart

* LVEF < 45% or major LV wall motion abnormality
# MAP < 60 mmHg, CVP > 12 mmHg, NA > 0.2 μg/kg/min

**Figure 1.** Proposed multi-organ donor management algorithm (echocardiogram available)
Conventional Management
• Adjust volume status: target CVP = 6-12 mmHg
• Adjust noradrenaline to keep MAP ≥ 60 mmHg (target noradrenaline dose ≤ 0.2 µg/kg/min)
• Correct acidosis: target pH = 7.35-7.45
• Correct hypoxaemia: target pO₂ > 80 mmHg, O₂ sat. > 95%
• Correct blood glucose: Insulin: 1 Unit/hr titrate to BGL 6-10 mmol/l

Stable Haemodynamics
• MAP > 60 mmHg
• CVP = 6-12 mmHg
• Noradrenaline ≤ 0.2 µg/kg/min

Unstable Haemodynamics
• MAP < 60 mmHg
• CVP > 12 mmHg
• Noradrenaline > 0.2 µg/kg/min

Hormonal Resuscitation (HR)
• Methylprednisolone: 15 mg/kg IV bolus
• Start Vasopressin: infusion 2.4 Units/hr
• T3: 4 µg IV bolus + infusion 4 µg/hr

Proceed with Recovery

Ongoing Haemodynamic Management
Adjust fluids and noradrenaline infusion rate at 15 minute intervals to minimise use of noradrenaline and meet the following target criteria:
• MAP > 60 mmHg
• CVP = 6-12 mmHg
• Noradrenaline ≤ 0.2 µg/kg/min

Criteria Met
• Recover Heart

Criteria Not Met
• Discuss with Heart Transplant Team

Figure 2. Proposed multi-organ donor management algorithm (echocardiogram unavailable)
associated with the following statistically significant increased probabilities of an organ being transplanted from a donor: kidney 7.3%, heart 4.7%, liver 4.9%, lung 2.8%, and pancreas 6.0%. Extrapolation of these probabilities to the 5,921 brain-dead donors recovered in 2001 was calculated to yield a total increase of 2,053 organs.

**Anti-inflammatory treatment of the brain-dead donor**

Another potential approach to improving the quality of cadaveric donor organs involves the use of specific or non-specific anti-inflammatory treatments aimed at blunting or reversing the up-regulation of proinflammatory cytokines, adhesion molecules and donor specific antigens. The administration of high dose steroids to brain-dead donors has been shown experimentally to improve survival of renal and cardiac allografts and clinically to improve donor lung function resulting in an increased number of transplanted lung allografts. It is noteworthy that the steroid doses of the combined hormone resuscitation protocols used in the above-mentioned studies were very high indicating that the “hormonal cocktail” is likely to be exerting an anti-inflammatory as well as hormone-replacement role.

**A standardised protocol for the intensive care unit management of the cadaveric multi-organ donor?**

Based on available experimental and clinical trial data reviewed above, UNOS and other stakeholders in the United States have now endorsed the use of haemodynamic monitoring and combined hormonal resuscitation in all brain dead donors who are haemodynamically unstable, require high doses of inotropic/pressor agents or who show evidence of impaired cardiac function on echocardiography. Brain dead donors who demonstrate one or more of these features probably account for between one quarter and one third of multi-organ donors. Invasive haemodynamic monitoring of these donors may be difficult to implement in the Australian and New Zealand setting, however the administration of the combined hormonal resuscitation protocol would not be.

Recently, we evaluated the hormonal resuscitation protocol recommended by Wheeldon et al and Rosengard et al in a pig transplant model in which animals were supported for 6 hours after the onset of brain death. When combined administration of methylprednisolone, vasopressin and tri-iodothyronine was commenced at 3 hours after onset of brain death, all animals were able to be weaned from noradrenaline, whereas control animals required escalating noradrenaline infusion rates to maintain a target systemic mean arterial pressure above 70 mmHg. Left ventricular contractile function as measured by preload recruitable stroke work was significantly better in the hormone-treated animals at 6 hours after brain death. On a practical note, the hormonal resuscitation protocol was simple to administer requiring a bolus intravenous administration of methylprednisolone and the commencement of continuous infusions of vasopressin and tri-iodothyronine. Based on our experimental observations with hormonal resuscitation we have adapted the donor management protocol developed by Rosengard and colleagues to one which we believe can be applied in intensive care units broadly across Australia and New Zealand. Two algorithms have been developed, one for instances where echocardiographic evaluation of the donor is available (Figure 1) and one for instances where echocardiography is unavailable (Figure 2).

**Conclusions**

At present, there is no consensus regarding the intensive care management of the brain-dead multi-organ donor. The implementation of a standardised management protocol across Australia and New Zealand would markedly simplify this aspect of donor care. Furthermore, available evidence suggests that the routine administration of combined hormonal resuscitation to the one third of donors who are haemodynamically unstable is likely to increase the yield of all transplantable organs from these donors.

The authors acknowledge and thank the State Liaison Group NEW SOUTH WALES and A.C.T. for their input and help in the development of the donor management algorithms.

**A. HING**
Heart and Lung Transplant Unit, St Vincents Hospital, Victor Chang Cardiac Research Institute, NEW SOUTH WALES

**M. HICKS**
Department of Clinical Pharmacology, St Vincent’s Hospital, School of Physiology and Pharmacology, University of New South Wales, NEW SOUTH WALES

**L. GAO**
Transplantation Research Laboratory, Victor Chang Cardiac Research Institute, NEW SOUTH WALES

**M. WILSON**
Heart and Lung Transplant Unit, St Vincents Hospital, Victor Chang Research Institute, NEW SOUTH WALES

**F. MACKIE**
LifeLink Organ Donation Network NEW SOUTH WALES and A.C.T
P. S. MACDONALD  
Heart and Lung Transplant Unit, St Vincents Hospital,  
Victor Chang Cardiac Research Institute, NEW SOUTH WALES

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Use of continuous positive airway pressure for acute severe dyspnoea in the pre-hospital setting?

Acute pulmonary oedema (APO) is a life threatening illness with patients often being admitted to hospital and treated with continuous positive airway pressure. Continuous positive airway pressure (CPAP) increases functional residual capacity, improves lung mechanics and reduces work of breathing. The increase in intrathoracic pressure reduces preload and afterload and mean transmural filling pressures have been shown to fall, suggesting improvement in cardiac performance, all of which benefit patients with APO.
Bersten et al.,4 studied 39 patients with severe cardiogenic pulmonary oedema. They randomly allocated patients to receive oxygen alone or oxygen with CPAP. Patients in the CPAP group had a significantly lower need for intubation and ventilation (0 vs 35%) and a trend to lower mortality, although this failed to reach statistical significance (11% vs 20%). Lin et al.,5 randomly allocated 100 patients to receive oxygen or CPAP plus oxygen. There was a statistically significant lowering of intubation rate in the CPAP group (16% vs 36%) but only a slight trend to lower mortality (8% vs 12%). Rasanen et al.,6 in 40 hypoxic respiratory failure patients without hypercapnia or acidosis who were randomly assigned to receive CPAP or oxygen, reported a trend to lower mortality which once again failed to reach statistical significance.

Because of its ease of administration, CPAP is now being considered in the prehospital setting. Kosowsky et al.,7 reported a prospective case series in which paramedics applied CPAP to patients they believed to have APO and who were in imminent need of endotracheal intubation. Nineteen patients received CPAP, 13 of whom were subsequently diagnosed as having APO. Alternative diagnoses were chronic obstructive pulmonary disease (3 patients), pneumonia (2 patients) and intracerebral haemorrhage (1 patient). Four of the 13 patients were subsequently intubated in hospital. Three patients with non-APO diagnoses required intubation. Hastings et al.,8 in a six month observational trial of CPAP in 32 patients with a pulse oximetry recording < 90% and in whom the paramedic thought had APO, reported only one patient (3%) who required intubation in the field and none of the remaining 31 patients requiring intubation at hospital. A retrospective review suggested that prior to the introduction of CPAP, 20% of such patients would have been intubated in the prehospital setting.

Kallio et al.,9 in a one year observational study of 116 patients receiving CPAP in the prehospital setting, reported 2 patients requiring prehospital intubation and 6 patients subsequently requiring intubation in hospital. The diagnosis of APO was verified in 69% of cases. Alternative diagnoses were COPD, pneumonia and subarachnoid haemorrhage. Treatment with CPAP, intravenous nitrate and intravenous morphine resulted in improvement of oxygenation, respiratory rate and heart rate. No complications of CPAP therapy were noted. Templier et al.,10 used a Boussignac CPAP system for APO in 57 pre hospital patients with acute respiratory distress. Respiratory rate and pulse oximetry improved following application of the CPAP. Gardtman et al.,11 described the introduction of a new intensified treatment for APO which included CPAP, nitroglycerine and frusemide. Historical controls were used. There was a reduction in the number of patients with fulminant pulmonary oedema on arrival at hospital (76% vs 93%) and a reduction in median CK-MB levels in the period with new intensified treatment. There was no improvement in mortality either immediate or at one year follow up.

Acute exacerbation of chronic obstructive pulmonary disease (COPD) is a common prehospital cause of acute shortness of breath and CPAP has been used in the hospital setting for its management to reduce work of breathing by reducing inspiratory threshold work.12 While there are numerous uncontrolled reports of the use of CPAP with benefit in patients who have an acute exacerbation of COPD, exacerbation of dynamic hyperinflation and barotrauma are the principle concerns of the use of CPAP in these patients.13 Asthma is another common prehospital cause of acute shortness of breath and there are a small number of laboratory and clinical reports which document improvement in breathlessness and work of breathing with mask CPAP, although none report a reduction in mortality.13

In conclusion, CPAP is a well established in-hospital treatment for severe acute pulmonary oedema and the above reports suggest that it is unlikely to cause major harm to patients with acute severe dyspnoea suffering from other conditions in the prehospital environment. Prehospital trials have suggested a benefit with CPAP but none have been conducted with matched or randomised controls. These studies would now appear to be warranted.

S. BAKER
Senior Lecturer, Department of Health Sciences, Flinders University, Bedford Park, SOUTH AUSTRALIA

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The role of the ICU research coordinator in Australia: an invaluable resource for ICU research

A recent development in the staffing profiles of many Australian Intensive Care Units (ICUs) has been the addition of the Research Coordinator (RC) positions (also termed Research Nurse/Officer or similar). At least 70 such positions now exist throughout Australia and New Zealand. Although there have been reports of the RC role in other specialties and countries, the role in Australian ICU research has not previously been described in the professional literature. The novelty of the ICU RC position, combined with a lack of discussion in the literature, may mean that other health professionals poorly understand the role. In some settings, the RC role has been noted to be sometimes misinterpreted as limited to being a “doctors’ lackey”, performing mindless data collection for medical research or alternately as an elitist academic far removed from clinical relevance. In actuality, the role is neither of these things, being both complex and clinically based, it requires specialised knowledge and skills in order to undertake, promote and manage quality ICU research activity. This review seeks to document the development of the ICU RC role in Australia and to provide factual information regarding the role.

LITERATURE REVIEW

A search using the terms “Research Coordinator”, “Research Nurse”, and “Trials Coordinator” in the databases Medline and CINAHL identified 71 articles which focussed on the RC role. The earliest reports of the RC role emanated from the United States of America in the 1970’s. The majority of published literature pertaining to the RC role consists of anecdotal reports from RCs in a variety of clinical settings, most frequently oncology and cardiology. Whilst the data provided is descriptive, there is a significant degree of commonality amongst the reported themes:

- Coordination of pharmaceutical industry sponsored trials is the cornerstone of the RC role, although this may vary depending on the research interests of the employing department and of the RC.
- The RC facilitates scientifically rigorous research, drawing upon a high level of knowledge regarding research methodology and a commitment to thoroughness at all stages of the research process.
- The RC ensures ethical research practice by advanced knowledge of local and international legislation and norms regarding protection of research participants.
- Nursing knowledge and skills are valuable within the RC role, particularly specialist clinical knowledge and skills, health promotion and education, patient advocacy, and liaison and coordination of the health care team.

There are no published reports of the role of RCs in Australian ICUs. However, reports of critical care RCs have emerged from emergency/trauma departments in the USA, Australia, a New Zealand coronary care unit, and ICUs in the UK, USA and South Africa. The descriptions of the RC role in critical care are slightly different to those in non-critical care. In critical care areas more emphasis is placed on involvement in departmental (local investigator initiated), rather than sponsored pharmaceutical research. Reports of RC activities involving literature reviews, protocol development, and the analysis, presentation and publication of results are more evident in the critical care

setting.\textsuperscript{3,7,11,12,14} There is also a greater recognition of the role in a broader research context. That is, to undertake research, but also to teach research methodology to others, and to assist with the interpretation of research findings and their implementation into evidence based practice.\textsuperscript{8} Obtaining informed consent for research in the unconscious and/or intubated patient is a specific challenge for the RC in critical care areas.\textsuperscript{12} Additionally, unique to the critical care setting is the need for RCs to be available twenty-four hours a day, seven days a week to screen and recruit patients.\textsuperscript{7,8} In contrast, non-critical care RCs frequently cite the satisfaction of working standard business hours.

Formal research into the RC role has been limited, with only six studies reported in the literature. Of these, four used quantitative methodology including self-report surveys of Spanish\textsuperscript{15} or American\textsuperscript{16,17} RCs and a time-in-motion study from Canada.\textsuperscript{18} Two investigations were of a qualitative approach, using semi-structured interviews and field work.\textsuperscript{19,20} Research topics have included demographics, educational preparation, role activities, reasons for seeking the position, positive and negative aspects of the role, and overall job satisfaction. The Canadian investigation of the proportion of time spent on various activities was the only study including ICU RCs, and this is to date only published in abstract form.\textsuperscript{18}

THE ICU RESEARCH COORDINATOR IN AUSTRALIA

Historical Development

The advent of RCs in Australian ICUs seems to have occurred in the mid-1990s. Prior to this, ICU research was predominantly single-centred; instigated and managed by local Intensivists with a research interest. Pharmaceutical development trials were uncommon, of simple design compared to today’s standards, and were able to be managed by the Intensivist with occasional assistance provided by other medical or nursing staff. Opportunities for nurses to work in research had traditionally been limited to university, or hospital-based, rather than ICU-based positions.

Three important developments in the 1990s may be seen as historically important in the genesis of the RC role in Australian ICUs. Firstly, the decade saw a rapid increase in the number of clinical trials instigated by the commercial sector to evaluate new drugs in the clinical setting. This increased volume of work was combined with an increase in the magnitude and complexity in the regulatory requirements of the Australian Therapeutic Goods Administration (TGA) and the National Health and Medical Research Council (NHMRC). On a global level, the International Council of Harmonization’s (ICH) Good Clinical Research Practice (GCRP) Guidelines further added to the increase in paperwork required to conduct clinical research. The management of pharmaceutical trials within the clinical setting had progressed beyond that which medical staff could integrate into their clinical and other workloads on a part-time basis. The pharmaceutical industry became more insistent that part of the funding for each of the clinical trial be used to secure a dedicated staff member to manage the overall conduct of the research.

Secondly, the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG) was formed in 1994 with the aim of conducting high-quality, large-scale randomised controlled trials (RCTs) in intensive care (www.anzics.com.au). This group has seen a rapid growth in the quantity and quality of multi-centre ICU research, to the point where recent studies such as the Saline versus Albumin Fluid Evaluation (SAFE Study)\textsuperscript{21} have attracted significant research grants, which have further generated the demand and funding for RC positions.

A third factor in the proliferation of the RC role has been the increasing growth of the evidence-based practice movement in healthcare. This development has witnessed a greater number of health professionals educationally prepared to undertake research and a health system more receptive to the commitment of funds to research positions. The combined effect of these historical developments has created the opportunity to implement ICU RC positions, which have predominantly been filled by ICU nurses.

In 1998, it was recognised that RCs employed in ICUs were often working in isolation, meaning a lack of opportunities for shared problem-solving, brainstorming of new ideas, or even peer-support. The face-to-face and electronic communication fora of the ANZICS CTG assisted somewhat in increasing the exposure of Australian ICU RCs to each other. Following discussions over several months, the ICU Research Coordinators Interest Group (IRCG) was developed and formalised in March 2000. The aims of this group are to provide collegial support for ICU RCs, to foster multi-centre ICU nursing related research, to liaise with the CTG, and to provide input into formulation of study protocols and “case record forms”.

After the first decade of the role’s existence, Australian ICU RC positions are now well established in Level III units, with numbers also growing in Level II units. IRCIG currently has 70 subscribers to its mailing list from throughout Australia and New Zealand. In combination with the non-listed RCs the total cohort is probably approaching 100 (J.Foote, IRCIG Listmaster, personal correspondence, 10 August, 2004).

The Research Coordinator role in Australian ICUs

The RCs work in a multi-disciplinary environment,
which provides the opportunity to perform research in a wide variety of fields as diverse as ventilation therapy, sepsis, neurosurgery and pain management. They may collaborate with a range of researchers from all the health professions, in addition to those from scientific, statistical, and social science backgrounds.

Due to the influence of the ANZICS CTG, pharmaceutical trials are rarely the sole focus of ICU research activity. In fact, the RC typically works on multiple concurrent studies including pharmaceutical, CTG, and departmental-initiated research. The RC’s role is to develop a research plan in each study and may vary from minor administrative or data collection assistance, to significant research design and coordination responsibilities, or anything in between. Alternately, the RC may provide only an advisory role. The extent of the RC’s involvement is negotiated on a project-by-project basis depending on the nature and complexity of the study, the experience of the investigators, priority of the research topic, and pre-existing RC workloads. The RC works closely with the ICU senior medical staff, particularly the designated “Director of Research” or Site-Investigator (S-I). The S-I is usually a senior medical specialist who, in addition to research, has a clinical and administrative workload. The actual research managed by the RC varies depending on the unit and the interests of the S-I, RC and those ICU staff who are active in research.

Pharmaceutical Trials

For most RCs the cornerstone of their work is coordination of clinical drug trials sponsored by the pharmaceutical industry. Funding derived from this provides the departmental infrastructure or platform, upon which local researchers can undertake their own research. For each trial the RC and S-I assess the protocol for feasibility, considering the admission patterns and clinical practice within the unit. If the project proceeds, the RC will work with the pharmaceutical company representative to prepare the necessary documentation. The application to the institutional Human Research Ethics Committee (HREC) is time-consuming, requiring not only administration but developmental work such as the adaptation of overseas-designed Patient Information Sheets and Consent Forms to locally appropriate language and standards. RCs must have advanced understanding of research legislation and standards. These include: local HREC requirements, the National Statement on the Ethical Conduct of Research, pharmaceutical industry processes, the Therapeutic Goods Administration’s directives for Good Clinical Practice (GCP), and State/Territory legislation pertaining to consent.

Before the trial commences, the RC and S-I attend a “Start-Up” meeting to receive study specific training. A Site Initiation Visit is undertaken by the pharmaceutical company to ensure appropriate standards are in place. The RC will conduct staff education on the new medication/device to ensure that clinical staff are familiar with the product, effects and possible side effects, special procedures and what to do in case of a drug/device-related emergency. The RC will then commence screening patients for suitable participants by assessing admission diagnosis, past medical history and clinical data to establish whether the trial inclusion and exclusion criteria are met. The RC may participate in the consent process once a suitable patient has been identified, but most importantly ensures that both protocol and GCP are followed. Most trials require blood and tissue sampling, necessitating the RC to obtain samples, process the material (centrifugation and/or slide preparation) and courier it appropriately under legislation governing the transfer of biological material. The RC administers or monitors administration of trial medication, and accounts for drug supply, storage and dispensation in conjunction with the Pharmacy. Finally, the RC completes required study documentation, usually consisting of multiple clinical parameters over an extended period of time, to assess drug efficacy and safety. Such data is often subject to further clarification by the pharmaceutical company, in which case the RC will respond to data queries. Regulatory authorities and/or sponsors may audit the ICU for adherence to research standards. The RC must be able to not only vouch for but provide documentary evidence of compliance throughout the trial.

Departmental Research

Many RCs work in a unit where staff conduct their own research. Unlike pharmaceutical trials, these projects must be developed from the beginning by the department. In addition to the responsibilities typical in pharmaceutical research, departmental projects may require the RC’s involvement in literature searches, drafting protocols, developing data collection tools, contacting potential participants, arranging hospital visits and liaising with other hospital and university departments. Departmental trials may involve several centres and the RC may manage the added administration required for the research to be conducted identically across all sites. When all data collection has all been completed, the RC may collate the data, assist in statistical analysis and participate in presenting the results locally as well as at scientific meetings and for publication.

RC-led research

Many RCs see their position as an opportunity to develop their own research ideas or work with their colleagues to develop research proposals and conduct
trials either in their own institution or even as a multi-centre study extended across several sites. RC-led research has been successfully completed and published,24-32 with an encouraging recent development being the first multi-site trial undertaken by six ICU RCs.33 Presentations at the 2004 Australian and New Zealand Annual Scientific Meeting on Intensive Care also evidenced the research skills and professional commitment of RCs. At least 7 of the 30 Nursing and Allied Health free papers presented consisted of original research conducted by RCs as chief investigator. These presentations were in addition to other work presented where RCs fulfilled a co-investigator role. Undertaking personal research can promote career development, fulfil the requirements for a university qualification, and enhance job satisfaction for RCs.

Outside the ICU

Some RCs also work in the animal laboratory. A specialist ethics application must be completed and relevant staff, including the RC must have completed an animal ethics course. Animal laboratories are often located off campus posing logistic challenges, and close collaboration with the laboratory staff is essential. The sequence of experimental events must be anticipated so that all necessary equipment is available in the laboratory prior to commencing the experiment. Animal research requires the RC to use clinical skills including aspects of ICU, anaesthesia and operating room nursing. There are many unique challenges associated with animal work, which calls for lateral thinking by the whole team, such as venous access and intubation, delivery of anaesthesia and maintaining physiological parameters. And last, but not least there is the sensitive issue of euthanasia at the end of the experiment to be dealt with.

The role of the RC may include involvement with unit audits and presentation of audit results, application for research grants, coordinating meetings between different research departments, conducting education sessions for nursing and medical staff on research related topics and produce the annual research report. There is an ongoing need to maintain professional knowledge by attending courses, meetings and conferences; and to keep abreast of new developments reported in the literature. The RC may engage in professional committees both at local and national level, and assist in relevant clinical policy reviews and development. An RC representative is currently active in both the ANZICS CTG and the Australian College of Critical Care Nurses’ Research Advisory Panel (ACC CN RAP).

CONCLUSION

The Australian ICU RC role is relatively new; however, continually increasing RC numbers and research strength of the ICU community suggest that the position is here to stay. The position offers incumbents the opportunity to develop specialist knowledge and skills in clinically based ICU research. Positive attributes of the position include a high degree of autonomy, opportunities for personal achievements and novel experiences. The next stage of role development for RCs would seem to be formalisation of the role in terms of recognised position descriptions, key-selection criteria, organisational structures, and promotion of this unique careerpath. Attaining job security for longer than the currently prevalent short-term contracts is an issue. Access to appropriate training, ongoing education and support also remains a challenge. Many current RCs in Australian ICUs are holding the inaugural position in this professional role, which has yet to be streamlined. Greater recognition of the RC role would ensure job satisfaction, security and productivity for RCs and ensure colleagues understand that the role is neither “Doctors’ Lackey” nor “Ivory-Tower Academic”, but rather a valuable resource for rigorous and ethical ICU research.

Disclosure

The authors wish to emphasise that this article is based on literature and personal experience and does not necessarily reflect the situation for all other Australian ICU RCs. The authors have undertaken ICU RC position for periods in excess of 8 (BR) and 4 (CR) years respectively.

B. ROBERTS

Department of Intensive Care, Sir Charles Gairdner Hospital, Perth, WESTERN AUSTRALIA

C. M. RICKARD

School of Rural Health, Monash University, VICTORIA

REFERENCES