Editorials

Renal protection and salvage: precise answers require precise questions

Disagreement over patient management is often based upon an absence of fact, and this has been typified by approaches to renal protection and renal salvage. Once several prospective randomised clinical trials (PRCT's) demonstrate the same principle, a new fact is 'established'. This requires generation of a sound hypothesis, usually derived from basic research into pathophysiological mechanisms, followed by extremely careful study design. However, this paradigm is better established in some disciplines than others, and using thrombolytic therapy in myocardial infarction as an example, this can almost become an art form.

As Duke points out,[1] there are few established facts that help us manage acute renal dysfunction at the bedside. However, while some clinicians and scientists saw the potential of thrombolytics in the 1960's and 1970's, it has taken a massive injection of energy, funding and patients to establish the role of these drugs in current practice. While a similar research strategy is unlikely to be undertaken into acute renal dysfunction, we can learn and progress through an improved understanding of its basic mechanisms, and hence develop, test and empirically use therapeutic strategies.

Research into the basic mechanisms underlying acute renal dysfunction over the last 10-15 years has exposed a number of important themes. Many of the early animal models were not relevant to clinical practice. Tubular obstruction is rarely found on renal biopsies, which generally show minor histological changes. Consistent with the medullary ischaemia model championed by Brezis and Epstein,[2] this is because the well perfused renal cortex is usually sampled, with medullary biopsies showing far more impressive ischaemic changes.[3] Renal ischaemia may result from both hypoperfusion or an unsatiated increase in the metabolic work required to reabsorb solute in the distal tubule. Also particularly germane to critically ill patients, is clear evidence of synergistic injury when activated neutrophils, as is seen in sepsis and many cytokine-mediated states, are now added to hypoperfusion.[4] Finally, the homeostatic response to renal ischaemia must be either to augment flow or to reduce metabolic work. Tubuloglomerular feedback reduces medullary work by coupling glomerular filtration rate (GFR) with tubular reabsorptive capacity. Its primary mediator appears to be adenosine which acts to reduce filtration of solute, and hence its active reabsorption, by afferent vasoconstriction.[5]

With these mechanisms of renal injury and dysfunction in mind, well designed studies would also then need to optimise both haemodynamic support, in order to optimise renal blood flow, and the timing or window of intervention. Pre-emptive therapy in haemodynamically stable patients has been studied, with promising results. Radiocontrast nephropathy is a reproducible ischaemic insult which is ameliorated with the adenosine antagonist theophylline.[6] Pre-emptive administration of calcium channel antagonists also reduces renal dysfunction following renal transplantation.[7] However, the coal face of critical care medicine rarely allows pre-emptive therapy, rather we are left with windows of progressive renal insult, injury and dysfunction.

An example of the importance of timing of intervention has been the investigation of frusemide. There is clear evidence that pre-emptive inhibition of distal tubular sodium chloride reabsorption ameliorates ischaemic injury and renal dysfunction in animal models. This is not due to increased tubular flow or resolution of tubular obstruction since similar results are not found with proximal tubular diuretics that also fail to improve medullary oxygenation. However, most clinical studies have investigated the late administration of frusemide, in established renal failure, with predictably negative results.[8] A more relevant study would be to examine frusemide early in the course of renal injury in the presence of well defined haemodynamic support.

A recent PRCT examined anaritide,[9] an atrial natriuretic peptide analogue, since these factors may augment glomerular capillary ultrafiltration pressure independently of renal blood flow through differential effects on the efferent and afferent arterioles. However, in our view the patients in this study did not have adequate haemodynamic support at study entry, and the systemic vasodilator effects of anaritide resulted in a further erosion of blood pressure. While this PRCT failed to show benefit, it would seem premature to discard this line of investigation. Perhaps a better conclusion from this study is that, in the absence of defence of renal perfusion pressure, anaritide was of no benefit.

Despite the absence of a PRCT, defence of renal perfusion pressure is the cornerstone of therapy aimed at renal salvage. In laboratory studies the renal autoregulatory threshold is measured at a mean blood pressure of 80 mmHg,[10] with the autoregulatory threshold for GFR greater than that for renal blood flow. A decrease in mean blood pressure from 80 to 67 mmHg results in a 20% fall in renal blood flow and a

30% decrease in GFR in healthy subjects.[11] Since over 60% of the patients in the anaritide study had a history of hypertension, which right shifts the renal auto-regulation curve, even higher pressures should have been targeted in these patients. However, in critically ill patients vasopressor catecholamines are usually required to achieve these targets, and many clinicians remain concerned that direct renal vasoconstriction may occur. This does not appear to be the case in the laboratory, and there is growing observational data that augmentation of renal perfusion pressure remains the single most effective strategy.[12,13]

The Australian and New Zealand Intensive Care Society Clinical Trials Group is bringing their first PRCT, examining low-dose dopamine in patients with SIRS, to its conclusion.[14] Many of the issues we have raised were addressed in this study (early intervention, haemodynamic goals), and yet it appears that another negative result will be recorded. While, factual progress was made, publication of this data will also signal a new era in study design examining interventions designed to ameliorate renal dysfunction. In the meantime, there are some aspects of resuscitation of the kidney that should raise little conflict.

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Regional care of critically ill children

The care and transport of critically ill paediatric patients is an important problem for smaller hospitals remote from larger tertiary paediatric centres and paediatric intensive care units. Analysis of risk benefit for these patients involves complex issues including quality of care, relative morbidity and mortality, and the risks and inconvenience of transport to major centres. Quality of care questions involve debate on the need for a critical mass of patients and maintenance of skills for all intensive care staff, including senior medical staff, junior medical staff, and nursing staff.

There can be no argument about where critically ill paediatric patients are cared for best. There is substantive evidence from thoughtful, objective, controlled trials in refereed journals to show that tertiary paediatric intensive care units have better outcomes for these patients.[1-3] One of these studies which supported the evidence[2] showed that low risk patients in tertiary units may have higher than expected mortality, but this was an isolated finding, and the result is excused by the author (e.g. 60% had incurable disease) and rebuked by others.[4] Shortcomings mentioned in the debate have been personal comments in an editorial[5] and a number of letters,[6-10] and these do not provide objective data to support any debate.

The dilemma for regional centres is clearly stated in a study from the Intensive Care Unit at Palmerston

North Hospital.[11] The study acknowledges that the severely critically ill are best cared for in tertiary centres. Unfortunately, the study does not clearly define the rules by which advice is sought for transport to the Auckland PICU.

It is clear that the debate needs to be widened. For some regional intensive care units, all critically ill children should be transferred. For other units, it is difficult to set the rules for transfer. The suggestion that any child who has or potentially will require ventilation for more than 12 – 24 hours appears reasonable,[6] but this timing has not been validated. In addition, the need for ventilation may be difficult to predict, and the need for intubation may be avoided by early referral to a tertiary centre. The argument setting rules for which patients can be safely cared for in a regional hospital has also yet to be successfully put, and these rules will vary between institutions. There are obviously patients who should be transferred, just as there are patients who can be treated locally and not transferred. In the light of available evidence, when there is doubt, it would appear sensible to err on the side of caution. The ready availability of dedicated paediatric transport teams predicates this argument. Risks of interhospital transport are now lesser issues, and transport should be provided by teams used to dealing with these patients.[12]

More data is required to be able to set guidelines for individual intensive care units. One tool for obtaining such data is the Paediatric Index of Mortality (PIM),[13] as used by the Palmerston North study. However, for the Australian and New Zealand Intensive Care Society (ANZICS) Paediatric Intensive Care Registry, valid comparison of outcome data between units using PIM requires a minimum of 20 paediatric deaths to provide acceptable confidence intervals (personal communication). As such, many small units are not be able to draw meaningful conclusions using PIM, and assumptions on quality of care cannot be inferred.

It is important for regional hospitals to recognise and acknowledge their individual abilities and limitations with regard to the care of critically ill paediatric patients. Units not able to establish limitations should follow more generic rules in the interest of patient safety. A relationship with a tertiary PICU is essential to set these rules, and to allow appropriate communication regarding advice on clinical care, prehospital stabilisation, and safe transport for individual patients.

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Echocardiography and the intensive care unit

Understanding the workings and moods of the heart is central to much of intensive care medicine. Two articles by Donovan and Colreavy in this issue of *Critical Care and Resuscitation* seek to incorporate echocardiography as a routine and essential tool in the critical care setting.[1,2] Their articles raise the issue of providing an in-house service and becoming less reliant on other hospital teams, be they cardiology, radiology or nuclear medicine based.

There is a need for more involvement by intensivists in an intensive care echocardiographic service as the modality is well proven in improving patient care - any review on this subject includes numerous references to such. The obvious challenges that arise are issues of training, technical/nursing support and equipment.

Training usually requires cooperation with other groups in the hospital, particularly those that are fearful of losing their perceived 'turf'. Yet the presence of a trained and experienced doctor during performance of the study greatly assists decision making, especially when speed is of the essence. Our non-intensivist colleagues usually see a great advantage in this as they are not compromised by leaving what they are doing at the time to attend to an urgent study in the ICU. The usual scenario consists of a technician performing a study with formal reporting occurring much later. However, echocardiography training requires an initial broad exposure and therefore cooperation within an institution yields the best results. Standards are important and as outlined in the article, the Cardiac Society of Australia and New Zealand's requirement of performing greater than 300, and the supervised reporting of greater than 600 echocardiograms is reasonable and a good model. A unit of 12 -16 beds with greater than 1200 admissions per year would provide more than 300 examinations per annum, particularly when combined with preoperative assessment of complex patients, attending to major trauma or attending to a postcardiac surgical intensive care unit. The number of transoesophageal echocardiograms (TOE) necessary for training may be different in the intensive care setting as most patients are intubated and sedated, the intensivist may also obtain experience in the operating theatre, and the examinations take much longer when the underlying pathology is not known.

Technical support is essential, not only in assistance with the examination, but also caring for a complex and expensive machine. Looking after the machine should not be underestimated, particularly when TOEs are performed. The intubated, unstable patient requires more than technical skills and intensive care units may be better assisted by a nurse technician; someone who is skilled and qualified in both professions. This can be an attractive career prospect and the result is a more efficient and less expensive investigation. Whether it is a technician or a nurse, the person must either possess or be in the process of obtaining the Diploma in Medical Ultrasound. The cost implications are obvious, as this necessitates a full-time salary.

Purchasing and maintaining a good quality echocardiograph machine is at first a daunting challenge but most hospitals do purchase such machines from time to time, and the critical care setting is more deserving than most. A machine and service are often available in other units where the patients have defined and usually single organ problems such as found in the operating theatre, coronary care unit or outpatient department. A patient with multiorgan failure of unknown diagnosis, and haemodynamic instability, can present a more demanding need. Purchase of a TOE probe, while adding considerably to the cost of a machine, is essential in the critical care setting. Although most studies will appropriately be transthoracic (TTE), the TOE offers numerous advantages in selected patients. The state of evolution on the introduction of echocardiography into standard intensive care practice is similar to that of some years ago when nephrologists organised renal replacement therapy in the unit, where now it is routinely managed by the intensive care unit team.

Donovan and Colreavy clearly outline the broad spectrum of benefits echocardiography brings to the critically ill patient, from assessing cardiac function and haemodynamic monitoring, to searching for a source of embolus. At times it precludes the need for a pulmonary artery catheter, at other times the two techniques augment each other. Many diagnoses are obtained only by echocardiography. The benefits continue to increase as the modality is used more and the operator develops expertise. To achieve competency in evaluating function as outlined in the article is only the beginning: critically ill patients have less known about their cardiac dysfunction whether it is secondary to severe sepsis, diastolic dysfunction of the left ventricle from long-standing hypertension, or abnormal systolic function in the patient with a subarachnoid haemorrhage. Possible detrimental effects of our therapy on cardiac function, therapy often prescribed for another organ system, need to be understood. For instance, the effects of high-dose catecholamine infusions on the myocardium is surely a major challenge in clinical practice. Echocardiography, particularly the use of well selected and accurate Doppler signals, is useful in unravelling these important challenges. Evaluation of left ventricular diastolic function is one of these frontiers, a better understanding of the right ventricle being another. Newer techniques like Doppler Tissue Imaging and harmonic imaging have to be assessed as to their role, if any.

Echocardiography is a privilege we should avail ourselves of as a routine measure in the quest for improving diagnostic ability, management and ultimately, patient survival.

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Intravascular volume control – in concept and in clinical practice

For most clinicians managing the hypotensive patient, right atrial pressure (RAP) and/or pulmonary artery occlusion pressure (PaOP) are often used as a broad guide to assess the cardiovascular 'preload' and therefore intravascular volume requirement during resuscitation.

Parkin in this issue of *Critical Care and Resuscitation* presents an insightful (and different) approach to intravascular volume control by suggesting one should consider determinants of systemic venous return (which includes mean systemic filling pressure) when considering the intravascular volume 'state'.[1] He derives the elusive *in vivo* measurement of mean systemic filling pressure as an analogue; P_{msa} = 0.96 x RAP + 0.04 x mean arterial pressure + c x cardiac output (where c varies from 0.3 in a large young patient to 1.2 in a small elderly patient), and suggests that this should be the object of control. He adds that a variable derived from the P_{msa} and the RAP can also be used to guide inotropic control.

The concepts and principles of this approach to the intravascular volume 'state' (as Parkin acknowledges) are not necessarily new, although their application to a bedside problem probably is. In a study of 10 critically ill patients with renal failure, on inotropic and/or vasoactive infusions and requiring veno-venous haemodiafiltration, the diafiltrate was measured but not specifically replaced.[2] Instead, all intravenous fluids were administered by a servo-controller on the basis of maintaining the P_{msa} to a set point (with the understanding that normal P_{msa} is 7 mmHg). During the study period of 601 hours during which 417 L of diafiltrate were lost, 406 L were replaced by the servo-controller with reference only to the P_{msa}. The patient's tonicity was controlled dialytically.

This clinical application of the 'Guytonian principle' is truly exciting. However, as Parkin points out, there are a few caveats. Firstly, in considering the above equation, the major influence to the P_{msa} value is the RAP, and one of the difficulties he encountered was the critical positioning of pressure transducers on the phlebostatic axis during and after patient movement. This is no minor problem. Indeed, it is not an infrequent problem when one tries to assess accurately and control the mean arterial pressure in postoperative cardiac bypass patients using a wider range (e.g. 60 - 90 mmHg) than that required to accurately assess and control the P_{msa}. One study found that a large number of intensive care nursing staff varied in their zero reference point by as much as 7 cm vertically, a discrepancy that persisted even after attempts to standardise their technique.[3] Secondly, patients with severe diastolic or systolic failure may require a higher target P_{msa} (although this would seem to be simply a matter of resetting the target point). In relation to the equation to guide inotropic therapy, disorders that produce a rise in pressure outside the right atrium (i.e. increased intrathoracic or intrapericardial pressure) resulted in a falsely low value and required exclusion before the value was used for inotropic control.

As many use the Swan-Ganz catheter to guide resuscitation (for better or worse[4]), I think that some may be left wondering what would have happened if Parkin had compared his group of 10 patients with a similar group who were managed using the PaOP as the controlling value.

Nonetheless, I find the clinical application of P_{msa} an exciting prospect, particularly in the servo-controlled management of replacement of fluid losses in the patient on continuous haemodiafiltration, with the understanding that accuracy of the zero reference is vital to the practical application of this measurement. When that can be achieved as a routine in critical care units, the use of this value I think will become more widespread.

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