

Editorials

***Critical Care and Resuscitation* the journal of the Joint Faculty of Intensive Care Medicine**

This is the sixth year for the journal *Critical Care and Resuscitation* which began in March 1999 as a digest of post graduate reviews on topics relevant to the management of critically ill patients. It was published by the Australasian Academy of Critical Care Medicine (AACCM), in part, to supplement the post graduate educational courses in intensive care medicine organised by AACCM.

Throughout the five-year gestation of the journal, things have changed. It soon became the primary Australian Intensive Care Medicine periodical for reviews, reports and research and a forum for current opinion in intensive care medical issues. However, some changes have been hard to manage. For example, the administrative workload has increased dramatically due to the increase in subscription rates, manuscripts for review and editing, advertising and journal formatting.

Following a meeting of the board of the Joint Faculty of Intensive Care Medicine (JFICM) and the chairman of AACCM, it was decided that AACCM would alter its function to become a publisher and organiser of postgraduate meetings on intensive care medicine. Much of the administrative work would be handled by the JFICM secretariat and the journal would become the journal of JFICM.

Importantly, this change extends the educational activity of JFICM to the Australasian Intensive Care Medical community.

There was unanimous agreement concerning these changes as the dovetailing of the two bodies, at least in concept, appeared to be almost seamless. So begins a new era for the journal *Critical Care and Resuscitation* and AACCM. We are excited about these developments and look forward to a relationship that we believe will enhance the training and accreditation of intensivists enormously.

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Vasopressors in cardiac arrest: we may never know!

For over a century, scientists have experimented with vasopressors in attempt to improve outcomes after cardiac arrest. A more detailed understanding of pathophysiology and receptor physiology has fuelled the debate, but unfortunately the relative certainty afforded by good clinical trials has been lacking. Many options have been canvassed, the most prominent being adrenaline (epinephrine) in various doses, and more recently vasopressin.

Why vasopressin?

Arginine vasopressin (antidiuretic hormone) is a naturally occurring hormone that interacts with a number of receptor types, and results in a complex series of responses. At lower concentrations (< 8 picogram/mL) predominant clinical effects appear to be related to its anti-diuretic effect, but at higher concentrations more significant effects can be seen on the cardiovascular system.¹ Vasopressin interacts with a number of specific receptors, which have been characterised as V₁ (vascular), V₂ (renal), V₃ (pituitary), OTR (oxytocin receptor subtypes) and P₂ (purinergic).²

The vasopressor effects of vasopressin appear due to a number of inter-related mechanisms: activation of V₁ vascular receptors, inactivation of ATP-sensitive K⁺ channels, blunting of the increase in cGMP induced by nitric oxide, decrease in the synthesis of inducible nitric oxide synthase (NOS) and potentiation of adrenergic and other vasoconstrictive agents.^{1,3} It is possible that in addition to vasoconstriction, vasopressin could have a number of other potential beneficial effects in a cardiac arrest scenario, including increased cardiac inotropy, increased blood flow to some organs, and secretion of ACTH (a V₃ receptor effect).²

Although limited in number and quality, human studies have evaluated the vasoconstrictor effects of vasopressin in a number of non-arrest scenarios,^{1,4} including septic shock (where vasopressin levels seem inappropriately low)^{5,6} and vasodilatory shock after cardiac surgery.^{7,8} In many of these scenarios, there is a pressor response at doses of vasopressin that do not seem to provide benefit in "normal" patients.⁸ Obviously caution is required when extrapolating from short-term benefits (e.g. increased blood pressure, coronary perfusion pressure), as reinforced by the increased mortality associated with the use of NOS inhibitors.⁹

In cardiac arrests, the blood levels of vasopressin are increased, although it was observed that survivors had

higher levels. This additional observation led to the use of vasopressin in animal and eventually human cardiac arrest studies.^{10,11}

A recently published study in the New England Journal of Medicine,¹² and an accompanying editorial¹³ have thrown down the gauntlet to those organisations that produce guidelines for cardiac arrest management. In this large European study,¹² the investigators evaluated the potential role of vasopressin as the initial vasopressor in the management of out-of-hospital cardiac arrests. Two doses of either vasopressin (40 units) or adrenaline (1 mg) were administered to patients who required vasopressor support (in accord with European Resuscitation Council guidelines). Across the board, on an intention to treat basis, there were no differences in rates of hospital admission or hospital discharge (see Table 1).

Two post-hoc observations, however did raise some interesting points. Firstly, there was a small but

significant increase in the hospital discharge rates with vasopressin using univariate analysis when the initial cardiac rhythm was asystole (4.7% versus 1.5%; Relative Risk 0.327, 95% Confidence Intervals 0.107 - 1.001; Number Needed to Treat = 32 [95% confidence interval 15 to 1200]). Interestingly, if this post-hoc observation was to be confirmed in an additional clinical trial (as suggested by the authors), to achieve 80% power it would require more than 500 patients per group. Secondly, the benefits associated with vasopressin seemed to be associated with patients who did not respond to vasopressin alone, but required additional management with adrenaline. This subgroup obviously excluded all patients who had responded to the first two doses of vasopressor, and these were the patients that still needed resuscitation at more than 25 minutes after the onset of cardiac arrest. There are a number of other factors that need to be discussed. For example:

Table. Comparison of human cardiac arrest studies using vasopressin (40 U) vs. adrenaline (1 mg) studies

	<i>Lindner</i> ¹⁰			<i>Stiell</i> ¹¹			<i>Wenzel</i> ¹²		
	<i>Out-of-hospital</i>			<i>In-hospital</i>			<i>Out-of-hospital</i>		
	Vaso	Adr	P	Vaso	Adr	P	Vaso	Adr	P
Number of patients	20	20		104	96		589	597	
Mean age (years)	64	66		70	70		66	66	
Witnessed (%)	65	60		78	84		77	80	
Initial Rhythm VF/VT (%)	100	100		20	16		38	42	
Ischaemic heart disease (%)	70	75		33	34		38	41	
Mean time collapse to ACLS (min)	6.5	6.1		3.2	2.5		14.9	15.6	
Admit hospital with pulse > 20 min (%)				43	40	0.60*	36	31	0.06*
Admit hospital (survive 1 h) VF/VT (%)	70	35	0.06†	54	61	0.90*	46	43	0.48*
Admit hospital (survive 1 h) PEA (%)				33	29	0.70*	34	31	0.65*
Admit hospital (survive 1 h) Asys (%)				37	31	0.60*	29	20	0.02*
Hospital discharge (%)				12	14	0.67*	10	10	0.99*
Hospital discharge VF/VT (%)	40	15	0.16†	25	33	0.55*	18	19	0.70*
Hospital discharge PEA (%)				9	10	1.0*	6	9	0.47*
Hospital discharge Asys (%)				6	8	1.0*	5	2	0.04†

Lindner 1997 (single dose), Stiell 2001 (single dose), Wenzel 2004 (2 doses). Vaso = vasopressin, Adr = adrenaline, PEA = pulseless electrical activity, VT/VF = ventricular tachycardia/ventricular fibrillation, Asys = asystole, ACLS = Advanced cardiac life support

* Chi square, † Fisher's exact test

- 1) This study was performed in a pre-hospital setting that cannot easily be reproduced in many countries throughout the world. All the communities involved in the study had physician-staffed emergency medical service units.
- 2) The time intervals to administration of drugs is long (mean of 8 minutes of untreated [no BLS] cardiac arrest, then 10 minutes more until administration of first dose of study drug).
- 3) As acknowledged by the authors, there were some disturbing trends towards increased likelihood of adverse neurological outcomes (eg. coma, and severe cerebral disability) in the survivors from the vasopressor group.
- 4) This study contradicts the earlier out-of-hospital study of ventricular fibrillation¹⁰ that started the ball rolling when it found dramatically improved short-term survival advantage with a single dose (40 Units) vasopressin (see Table 1).

As is often the case, this study ends up posing more questions than it answers. It may well be that a combination of vasopressors, rather than any single vasopressor, are of value in cardiac arrests, though at this stage we can still only guess at the nature, timing and dosage of each. If the arrest is of short duration (e.g. in-hospital), then either adrenaline or vasopressin seem appropriate,¹¹ but if the arrest is prolonged (including the out-of-hospital scenario) then a combination may be better. Of course we should remember that there is still no study demonstrating any benefit to any vasopressor above placebo in human cardiac arrests.

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Life without the PA catheter

Sooner or later in this new century the very last pulmonary artery catheter (PAC) will be floated. With editorialists using imagery such as 'The Arc of the Pulmonary Artery Catheter',¹ the clear implication is that time must inevitably run out for our old friend. Precisely when this will happen is less clear, bearing in mind that for years the PAC has been the subject of similar speculation.²⁻⁸ Today in 2004 no one really knows how close its trajectory has dropped towards the horizon, or even whether the zenith has been passed.

Bedside, flow-directed right heart catheterisation has been a practical proposition for over 30 years.⁹ For the intensivist, PAC insertion is a rite of passage and part of ICU culture.¹⁰ Sales of PAC's world-wide are in the multi-millions,^{11,12} with annual costs exceeding \$2 billion in the United States alone.⁸ In Europe acceptance has also been strong, although less uniform. For example, on one particular day in 1995, 12.8% of European intensive care patients had a PAC *in situ*, with prevalence in individual countries ranging from 4.1% to 29.4%.¹³ Its following in Australia has also been enthusiastic, although less well documented.

Measured and derived pressure and flow variables obtainable from the PAC provide indices of preload, contractility and afterload in both systemic and pulmonary circulations,¹⁴ numbers which are difficult to predict prior to insertion.¹⁵ Although these are mere surrogate indices based on a simplistic non-pulsatile hydraulic model, they are adequate to categorize circulatory perturbations, and can lead to changes in therapy in over 50% of cases.¹⁶ With modifications, the PAC can provide volumetric measures of right ventricular preload and ejection fraction,¹⁷ continuously updated cardiac output measurements,¹⁸ and real-time mixed venous oxygen saturations (SvO₂).¹⁹ We owe much of our knowledge of circulatory pathophysiology in critical illness to the PAC.

Despite these features, there has always been debate over whether PAC insertion and monitoring translates into outcome benefit.^{20,21} Initial evidence on this question was either retrospective or else based on low power prospective studies. It pointed to possible detrimental effects in acute myocardial infarction,²²⁻²⁴ and inconsistent benefit when inserted for pre-operative 'tuning' of vascular surgical patients.²⁵⁻²⁹ Subsequently, there were promising results in high risk surgical patients, where therapy guided by pre-operative PAC insertion aimed at supra-normal oxygen delivery appeared to reduce mortality and morbidity dramatically.^{30,31} However, here again there were methodological flaws,³² and the important management difference appeared to be simple fluid loading. In contrast, there was no benefit,³³⁻³⁶ or even excess mortality,³⁷ when goal-directed therapy was commenced post insult in broader groups of critically ill patients. However, none of these studies was of PA catheterization *per se*. Often patients in both limbs had PAC's.

Until 1996, there remained an entrenched perception that inserting a PAC was a good thing to do – as fundamental to intensive care practice as the cardiocatheter is to obstetrics. Consequently, a lack of physician support prevented adequate recruitment for prospective randomized trials, with or without goal-directed therapy.³⁸ However, Connors and colleagues changed all that.³⁹ Their prospective non-randomized cohort study appeared to show that in any of 9 major disease categories, PAC insertion in the first 24 hours increased 30 day mortality (odds ratio 1.24, 95% CI 1.03-1.49), mean length of stay and mean cost per hospital stay. An editorial in the same journal issue called for a moratorium on PAC use and a prospective multi-centre trial.³ Subsequently in a British single-centre retrospective review of over 400 patients, PAC insertion appeared not to influence mortality in either direction.⁴⁰ Statistical methodology was similar to that of Connors and colleagues, but with an improved PAC

propensity score. Meanwhile other investigators uncovered disquieting influences on PAC insertion rates,⁴¹ which included the patients' race and insurance status, and care by a non full-time intensivist.

As a result physician attitudes became more flexible, so that genuinely meaningful prospective randomised trials comparing outcomes with and without PAC insertion are now appearing. The first to be published was from the Canadian Critical Care Clinical Trials Group.⁴² These researchers studied nearly 2000 high risk surgical patients, half of whom were subjected to peri-operative 'goal-directed' therapy guided by PAC, while the rest were managed along standard lines with central venous access. There were no improvements in length of stay or organ failure rates, and no survival differences out as far as six months. More recently the French Pulmonary Artery Catheter Study Group randomised 676 patients with early shock or established ARDS or both to PAC insertion or not.⁴³ Echocardiography was used prominently in both groups, and specific treatment was at physician discretion. There were no significant differences in mortality on days 14, 28 or 90. Need for organ support and times in ICU and in hospital were similar. However, mortality differences could not be ruled out absolutely. At the achieved recruitment there was still a 5% chance of an undetected excess mortality of 7.8%, whereas reliable detection of a 5% mortality difference required nearly ten times as many patients.¹

At this point one might ask why we are not having the same debate about other monitoring tools of unproven value, such as pulse oximetry.⁴⁴ The answer is that by comparison, PAC usage is expensive, invasive, relatively labour intensive and more dangerous. The effort to yield ratio is vastly different. The learning curve is much longer, not just for safe insertion but for getting accurate and meaningful data, interpreting this correctly and making interventions appropriate to the information obtained.⁴⁵ In each of these areas the pitfalls are many.¹⁴ The PAC can even kill (although in good hands this is now rare), either from adverse events during and after insertion¹⁴ or from over-zealous attempts at goal-directed therapy.³⁷ In the risk-benefit continuum, intracranial pressure monitoring is perhaps a closer comparison.⁴⁶

So where does this leave us? Already in 2004 there are less invasive devices which separately or together can provide useable measures of preload, contractility and afterload. These include systolic arterial pressure variation (highly predictive of fluid responsiveness),^{47,48} transpulmonary thermodilution coupled with pulse contour analysis,⁴⁹ oesophageal Doppler,⁵⁰ echocardiography,^{51,52} and impedance thoracocardiography.⁵³ As with the PAC, these monitoring tools can assist in categorising circulatory perturbations as hypovolaemic,

cardiogenic, obstructive, and distributive (or combinations), and can track responses to therapy.

Even SvO₂, unique to the PAC, has been supplanted. Intended to detect global tissue hypoxia by acting as a surrogate for mixed venous oxygen tension, SvO₂ has so far failed as a therapeutic target in ICU populations.³⁵ In contrast, central venous oxygen saturation (ScvO₂) appears successful as an early therapeutic end-point in severe sepsis and septic shock, the key feature being earlier and wider availability in the 'golden hour'.³⁴

No doubt we need to see more data and have further debate before the PAC is finally laid to rest. However, momentum is building. Younger intensivists without their older colleagues' familiarity with, and attachment to, the 'yellow snake' will eventually move to less invasive more user-friendly tools. The process will be gradual rather than sudden. Meanwhile, the PAC will continue on as a monitoring tool which, like any other monitoring tool, has no intrinsic therapeutic value.⁵⁵ Benefit can only arise when appropriate indications for insertion are followed, when there is skill in generating, interpreting and acting on the data, when safe practice is adhered to and when removal is prompt.¹⁴

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Managing septic acute renal failure: “fill and spill”? “squeeze and diurese”? or “block Bax to the max”?

“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it”.

Max Planck

Acute renal failure (ARF) affects 5 - 7% of all hospitalised patients¹ and sepsis remains the most important

cause in Australian critically ill patients, where it accounts for more than 50% of cases.² Despite our increasing ability to resuscitate patients and support vital organs, the incidence and mortality of septic ARF remain high.² A possible explanation for this lies in our poor understanding of the pathogenesis of septic ARF and in the application of the wrong pathophysiological paradigms to guide our therapy.

In general, our understanding of the pathogenesis of septic ARF is affected by the lack of renal histopathological information in the human when the glomerular filtration rate decreases and oliguria develops. In the absence of such information, we rely on indirect assessments based on blood and urine tests which force us to "guess" what might be happening to the kidney. It is not surprising, therefore, that our understanding of septic human ARF has advanced very little in the last 50 years.

To overcome such limitations, animal models of ARF have been developed to enable more sophisticated and invasive measurements to be made. Unfortunately, as recently highlighted,³ these animal models have been based mostly on ischaemia-reperfusion injury or drug-induced injury. Neither model is relevant to septic ARF, and information obtained from such models may be misleading when applied to a septic patient developing ARF.

The traditional paradigm for septic ARF: haemodynamic changes

A dominant and worldwide paradigm derived from observations in animals and humans with hypodynamic or hypovolaemic shock (haemorrhagic, cardiogenic or even septic shock) is based on a belief that ARF is due to renal ischaemia/underperfusion.³ This construct implies that restoration of an adequate renal blood flow should be the primary means of renal protection in critically ill patients. Led by a paradigm of what the "organ resuscitation" should be and how flow should be increased, the school of "fill and spill" ("fill" the circulation and urine will "spill" into the bucket) developed, with a common therapeutic response to oliguria in a septic patient being to "fill the circulation".⁴ This activity is reasonably rewarding in a patient presenting to the emergency department with hypotension and invisible neck veins when in the supine position. Whether it is rewarding in a patient with a right atrial pressure (RAP) of 15 mmHg remains doubtful and may lead to life-threatening pulmonary edema (with an accompanying further deterioration in GFR). Surprisingly, no randomised controlled trials (RCTs) exist to either support or negate this paradigm in septic patients.

The second approach of "squeeze and diurese" to treat septic ARF is still based on the concept that ischaemia/underperfusion is the major pathophysiological

mechanism. The protagonists of this approach hold that once adequate filling has been achieved (typically RAP > 10 mmHg in a patient without cardiac disease) and the cardiac output has been confirmed to be preserved or increased, more is to be gained by increasing the mean arterial pressure, the driving force to renal blood flow, with vasopressors ("squeeze")^{5,6} This is often accompanied by the administration of loop diuretics to "paralyse the medulla and avoid ischaemia" and induce polyuria to simplify fluid management as the antibiotics take effect and the septic state abates. Interestingly, this approach is considered dangerous in North America but is reasonably popular in Australia. As with the "fill and spill" paradigm, no RCTs exist to either support or negate the "squeeze and diurese" paradigm in septic patients.

In the presence of sepsis the belief that renal blood flow (RBF) decreases significantly remains controversial. Some studies have concluded that RBF in sepsis might, in fact, increase,^{7,8} and so the effect on RBF in each case of hyperdynamic human sepsis is largely unknown. It is possible that, even though there is preserved or increased global renal blood flow in hyperdynamic sepsis, intra-renal redistribution of blood flow favouring the cortex may occur.⁹ Unfortunately, no studies with technology that allows continuous measurements of both medullary and cortical blood flow in humans with hyperdynamic sepsis have been performed. In a recent investigation by our group, using laser Doppler flowmetry to continuously monitor medullary and cortical blood flow in hyperdynamic septic sheep,¹⁰ we found that both medullary and cortical blood flows remain unchanged and that the administration of norepinephrine induced a significant increase in flows to both regions. These observations challenge the view that the medulla is ischaemic during hyperdynamic sepsis, although it highlights that haemodynamic factors are indeed at work, which can be modified by interventions which affect systemic blood pressure and cardiac output. Nevertheless, even though haemodynamic changes are important, they are likely to represent only part of the mechanisms responsible for loss of renal function.

In conclusion, renal hypoperfusion might be important in hypodynamic states but persistent renal underperfusion is unlikely to play a key role in the continued development of ARF during hyperdynamic resuscitated sepsis (i.e. the state seen in the majority of critically ill, septic patients with severe ARF).

A new paradigm for septic ARF: apoptosis

From the above discussion, we know that neither global nor intrarenal haemodynamic changes can be consistently shown to be the sole contributor to sepsis-induced ARF. There must, therefore, be other

mechanisms at work that are not haemodynamic in nature but may be immunological or toxic in nature. Sepsis is characterised by the release of a vast array of inflammatory cytokines, arachidonate metabolites, vasoactive substances, thrombogenic agents and other biologically active mediators. A large body of experimental data suggests that these mediators and neuroendocrine mechanisms might be involved in the pathogenesis of organ dysfunction in sepsis.¹¹ How they injure the kidney remains unknown, although one such mechanism might be apoptosis.

Apoptosis, is a form of cell death that is mediated by a genetically determined biochemical pathway and characterised morphologically by cell shrinkage, plasma membrane blebbing, chromatin condensation and nuclear fragmentation.^{12,13} Cells can die by one of two pathways: necrosis or apoptosis. Necrosis results from severe ATP depletion and leads to rapid uncoordinated collapse of cellular homeostasis. Apoptosis is an energy-requiring and genetically directed process.

There is now evidence to show that renal tubular cells die by apoptosis as well as necrosis in experimental models of acute ischaemic and toxic renal injury.¹² Jo and colleagues, have recently shown that apoptosis of tubular cells by lipopolysaccharide and inflammatory cytokines is a possible mechanism of renal dysfunction in endotoxaemia.¹³ Unfortunately, TNF blockade with monoclonal antibodies fails to protect the animal or kidney from apoptosis during endotoxaemia.¹⁴ Preliminary experimental observations by our group in septic sheep also show that after only three hours of sepsis, induced by an intravenous injection of *Escherichia coli*, there is strong expression of early phase pro-apoptotic proteins such as Bax (the proapoptotic protein responsible for mitochondrial injury).¹³ Clearly, it would be attractive to have therapies that can favourably modulate the development of apoptosis and a new paradigm might need to be considered and tested. Perhaps "block Bax to the max".

Anti-apoptotic therapy for septic ARF

Attenuating or blocking apoptosis in sepsis and ARF might sound far-fetched but it is not as far away from the bedside as clinicians might think.

Activated protein C (APC). Bernard and colleagues showed a significant decrease in the 28 day mortality (30.8% in the placebo group and 24.7% in the treatment group) in 1690 sepsis patients treated with recombinant human activated protein C (rhAPC).¹⁵ The efficacy of rhAPC in septic patients may due to its anticoagulation effect. However, a recent study by Joyce *et al*,¹⁶ showed that rhAPC directly modulated patterns of endothelial cell gene expression clustering into anti-inflammatory and cell survival pathways and modulated several genes in the endothelial apoptosis pathway, including the Bcl-

2 homologue protein (an inhibitor of apoptosis). More recently, Cheng and co-workers have shown that APC blocks p53-mediated apoptosis of human brain endothelium *in vitro* as it normalised the Bax/Bcl-2 ratio and reduced caspase-3 signaling.¹⁷ This study creates a new link between coagulation, inflammation, apoptosis and cell death and provides some insight into the molecular basis for the efficacy of rhAPC in systemic inflammation and sepsis.

Caspases inhibitors. Caspases are enzymes which play a key role in apoptosis, and caspase inhibitors have been developed as anti-apoptotic agents. Fauvel *et al*, developed an animal model which showed myocardial dysfunction after endotoxin administration.¹⁸ These investigators successfully used a broad-spectrum caspase inhibitor (z-VAD.fmk) and a specific caspase-3-inhibitor (z-DEVD.fmk) and demonstrated decreased myocardial dysfunction, reduced caspase activation and reduced nuclear apoptosis 2 hours after experimental endotoxaemia. Neviere *et al*, also used z-VAD.fmk from 4 to 14 hours after endotoxin administration in rats and showed that not only was there a reduced caspase activity and nuclear apoptosis but also endotoxin-induced myocardial dysfunction could be completely prevented.¹⁹ As myocardial dysfunction can be prevented by anti-apoptotic treatment it is possible that future studies will show that the kidney is another organ that may benefit from caspase inhibitors. However, the complexity of the balance of factors involved in apoptosis and the response to sepsis is highlighted by the possibility that caspase inhibition may actually cause harm.²⁰

Insulin and ARF. The use of aggressive insulin therapy aimed at achieving euglycaemia in critically ill patients has been shown to reduce mortality significantly in a single centre study of critically ill patients.²¹ Among the important findings of this trial was a dramatic reduction in the development of severe ARF. A possible explanation for this finding may relate to the immunomodulating effects of insulin,²² including a powerful anti-apoptotic effect,²³ and conversely to the fact that a high glucose concentration induces oxidative stress-mediated apoptosis in tubular epithelial cells.²⁴

Low-tidal volume ventilation and ARF. Ventilation of patients with the acute respiratory distress syndrome by means of a low-tidal volume strategy has been shown to reduce mortality.²⁵ The mechanisms for such reduced mortality, however, remain unknown. In a fascinating series of studies, Imay *et al*,²⁶ recently demonstrated that low-tidal volume ventilation might protect from ventilation-induced renal epithelial cell apoptosis by reducing Fas ligand-dependent pro-apoptotic activity in plasma.

N-acetylcysteine. N-acetylcysteine has been shown to attenuate contrast-induced renal injury in many

randomised controlled studies.²⁷ However, its mechanism of action remains unknown. Its effect on oxygen radical-induced inflammation and apoptosis may offer the correct explanation²⁸ and suggest yet another pathway to the attenuation of sepsis/inflammation-associated apoptosis.

Conclusions

Although haemodynamic factors are likely to play an important role in the pathogenesis of sepsis-induced ARF, other mechanisms are also at work, which include immunological, toxic and inflammatory elements. Among these mechanisms, apoptosis may be important. Indeed organ protective strategies recently reported in animal and human studies could work by inhibiting the development of the apoptotic cascade. Although the importance of prompt and adequate resuscitation with rapid and carefully monitored restoration of intravascular filling, cardiac output and blood pressure must not be neglected, it is possible that, as evidence accumulates for apoptosis as a major mechanism of organ injury, the paradigms currently used to explain ARF in sepsis will shift from acute tubular necrosis to acute tubular apoptosis (ATA) and our therapeutic approach will change accordingly.

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