Renal Protective Agents: A Review

G. J. DUKE
Intensive Care Department, The Northern Hospital, Epping, VICTORIA

ABSTRACT

Objective: *To review the role of drugs with potential benefit to renal function in critically ill patients.*

Data sources: *A review of articles published in peer review journals from 1966 to 1998 and identified through a MEDLINE search on kidney failure.*

Summary of review: *Acute renal failure in critically ill patients is characterised by ischaemic injury to the tubule and is potentially preventable. Many agents have been shown to benefit renal function in animal models of acute renal failure, but supporting human data are lacking. There is evidence to support the defence of extracellular volume (with volume loading) and renal perfusion pressure (with pressor agents) but there are no controlled trials. While there are limited data to support the use of mannitol and calcium channel blockers in renal transplantation there are no studies that have confirmed their benefit in critically ill patients. Controlled trials of frusemide, dopamine and mannitol do not support their routine use. All other agents have been inadequately studied.*

Conclusions: *The common factor in renal dysfunction and acute renal failure is tubular ischaemia. Prevention of this final common pathway is the chief goal of renal protection in critically ill patients. Despite the plethora of potentially beneficial drugs, volume loading and defence of renal perfusion pressure (and renal blood flow) with pressor agents appear to be the only reliable means of renal protection.* (**Critical Care and Resuscitation 1999; 1: 265-275**)

Key words: Renal failure, diuretics, intravenous fluids, catecholamines, frusemide, mannitol, dopamine, noradrenaline, adrenaline, theophylline, natriuretic peptides

Critically ill patients with acute renal failure (ARF) carry a mortality risk of 35% - 70% with the higher risk found in those with comorbidities, increased age, and oliguria.[1,2] ARF is an independent risk factor for post-operative morbidity and mortality.[3,4] On these grounds 'renal protection' is a clinically attractive concept and implies that renal failure is potentially reversible or preventable.

Although ARF in the acutely ill patient may result from vascular, glomerular, interstitial, or obstructive injury, ischaemic tubular injury is the final common pathway in the majority of cases. Ischaemic injury occurs beyond the proximal segments of the nephron, particularly in the ascending loop of Henle of medullary nephrons (mTAL cells).[5-7] Tubular injury initially produces a profound functional defect with alteration in sub-cellular architecture (e.g. brush border disruption), followed later by cell necrosis.[8] Characteristically, glomeruli, proximal tubules and cortical nephrons - often found in renal biopsies - are spared.[5,8,9] Sepsis-associated renal injury and many nephrotoxic agents (e.g. NSAIDs, cyclosporin, amphotericin, myoglobin and contrast media) have also been shown to induce medullary hypoxia.[10]

Tubular ischaemia readily arises because intra-renal flow distribution is heterogeneous and the tubular cells in the medullary region live in a marginally hypoxic milieu.[10,11] Furthermore, these cells have a high metabolic (i.e. oxygen) demand related to active reabsorbtion of sodium and maintenance of medullary hypertonicity. This explains the susceptibility of the thick ascending loop of Henle (mTAL) cells[10,12] (and possibly the distal, S3, or pars recta segments of the proximal tubule)[7,10] to ischaemia. Elevated oxygen extraction in chronic renal failure[13] may also explain the increased sensitivity of these patients to renal insults.

The kidney has (at least) two potent physiological protective mechanisms that minimise the risk of

Correspondence to: Dr. G. J. Duke, Intensive care Department, The Northern Hospital, Epping, Victoria 3076
(e-mail: gduke@tnh.vic.gov.au)

uncontrolled medullary hypoxia - namely, autoregulation and tubuloglomerular feedback. As a result the healthy kidney has an extraordinary ability to withstand significant insults,[14-16] particularly if they are unifactorial or short-lived. Multiple repeated insults are much more likely to induce renal dysfunction.[17,18]

Renal autoregulation involves numerous endogenous mediators (including prostaglandins, dopamine, nitric oxide, adenosine, angiotensin, and endothelin) which maintain renal blood flow (RBF) across a wide range of perfusion pressures. For example, in the face of severe hypovolaemia and systemic vasoconstriction, the kidney is able to prevent intra-renal vasoconstriction and even increase its share of the cardiac output.[14,16] Despite this potent intra-renal modulation of flow resistance in healthy subjects, the presence of critical illness (particularly sepsis[19]), the induction of anaes-thesia,[16] or recent renal injury,[20] impair autoregulation[21] and RBF becomes pressure-dependent.

Tubuloglomerular feedback (TGF) is a regional protective mechanism whereby each nephron is able to match its glomerular filtration rate (GFR) and thus ultrafiltrate flow with the reabsorbtive capacity of its tubular cells. In the face of a decrease in tubular reabsorbtive capacity and/or an increase in chloride (and sodium) delivery to the macula densa cells of the juxtaglomerular apparatus, potent hormonal mechanisms involving adenosine[22] reduce GFR and defend peri-tubular blood flow. This has a dual benefit. The potential loss of large amounts of sodium (Na^+) and water from the animal is avoided, and the reduction in GFR decreases tubular metabolic demand, thus minimising the risk of ischaemic tubular damage.

Medullary hypoxia and TGF activation are manifested clinically by the presence of reversible oliguria. With removal of the primary problem (e.g. hypovolaemia, hypotension, nephrotoxins, or intra-abdominal hyper-tension) tubular function and urine flow may be restored before significant damage or renal failure occur. If the primary insult is severe or persistent then ischaemic tubular damage is likely and this will be manifest as established ARF. The initial onset of oliguria may thus be considered as an appropriate physiological response to an ischaemic renal threat.

Whilst a normal or high urine output does not preclude the presence of significant renal damage, oliguria (i.e. < 0.5ml/kg/h) should be viewed as an early warning sign of potentially reversible renal dysfunction. The resolution of oliguria is an important, but not the sole indicator, of satisfactory resuscitation in all forms of shock.

In the absence of more reliable and more sensitive indicators of early renal dysfunction, continuous urine output measurement remains one of the most useful, minimally-invasive, simple, and inexpensive clinical indicators of renal perfusion and medullary oxygenation. Other renal indicators such as serum markers (e.g. urea and creatinine), estimates of GFR (e.g. creatinine clearance, ^{99}Tc-DTPA excretion[23]), and measurement of RBF (e.g. ultrasound, nuclear medicine, renal thermodilution catheters[24]) are also useful in certain situations.[25] The use of 2 or 4 hour creatinine clearance measurement is a useful estimate of GFR[26] when urine output and serum markers are misleading. However, these renal monitors are limited by problems of poor resolution, slow response time, poor sensitivity, limited availability, or significant expense.

On *prima facie* grounds, the administration of tubular or osmotic diuretics in the presence of oliguria appears an attractive option. Diuretics reduce tubular metabolic activity,[10] reverse oliguria and may convert oliguric- to polyuric-ARF (which has a lower mortality).[27,28] Against this must be weighed the evidence that diuretics blunt TGF and reverse oliguria without addressing the primary problem, together with a conspicuous lack of favourable outcome data.

Diuretics with a selective proximal tubular site of action may adversely affect medullary oxygenation by increasing Na^+ load to the medullary tubular segments. The use of diuretic or osmotic agents removes the convenience and utility of urine output measurement as a guide to renal perfusion[25] and tubular 'well-being'. Furthermore, the absence of oliguria may create a false sense of security, particularly in critically ill patients where end-points for resuscitation of blood volume, cardiac output and organ perfusion are difficult to define even with invasive haemodynamic monitoring.[29]

Prevention and reversal of tubular ischaemia should be the primary goal of strategies for renal protection. The ideal renoprotective agent, particularly in critically ill patients, should provide tubular cytoprotection by: 1) maintaining tubular oxygen supply; 2) reducing tubular oxygen demand; 3) supporting physiological protective mechanisms (i.e. autoregulation and TGF); 4) producing little or no interference with clinical monitoring of renal function (e.g. urine output, serum markers), and; 5) being administered simply and inexpensively. Unfortunately few, if any, of the currently available (and alleged) renoprotective agents fulfil these criteria.

A number of drugs from divergent sources have

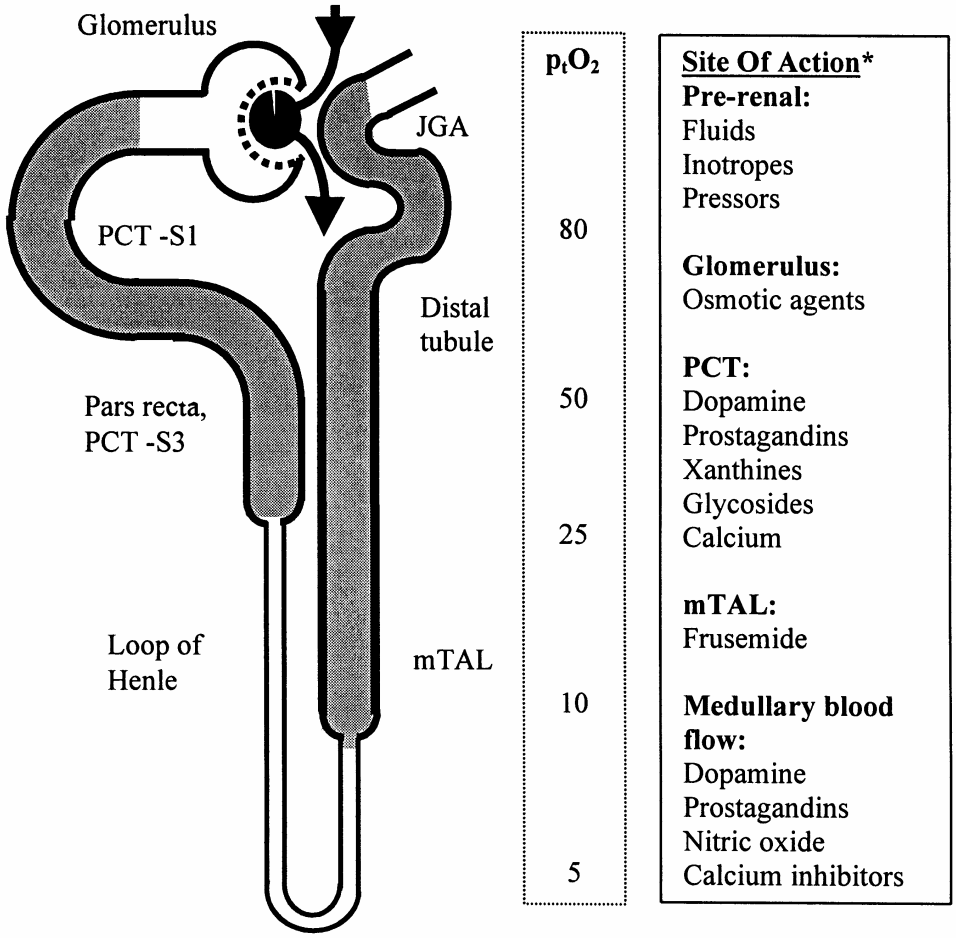

Figure 1. Diagrammatic representation of inner cortical nephron components and *possible site of action of renoprotective agents. PTC = proximal tubule, mTAL = medullary thick ascending loop of Henle, DTC = distal tubule, JGA = juxtaglomerular apparatus, P_tO_2 = tissue partial pressure of oxygen. Shaded area = high metabolic rate.

been claimed to afford renoprotective properties (Figure 1).

Many of these agents have also been shown to improve medullary oxygen tension and provide cytoprotection in vitro. Many have shown promise in ischaemic (e.g. renal artery clamp, intra-renal noradrenaline) and nephrotoxic (e.g. mercuric chloride, glycerol) models of ARF, given either prior to, or shortly after, the renal insult. Why then is there so little clinical evidence to support their use?

Laboratory models of ARF show little similarity to the clinical situation, where multiple and/or continuous insults exist rather than a single brief injury. Clinical research is dogged by problems of limited power (e.g. small sample size), poorly controlled variables, soft end-points, and lack of uniform outcome criteria. The absence of conclusive scientific data means that the clinical role, if any, for many potentially renoprotective agents remains unclear. Some of the more important or commonly used agents (Table 1) are discussed below.

Frusemide

Frusemide inhibits chloride reabsorption predominantly in the ascending loop of Henle, involving prostaglandins and dopamine as intermediate messengers. It was one of the earliest and most commonly used drugs purported to have renoprotective properties.

Initial enthusiasm for frusemide was based on evidence of 1) renal vasodilator properties in animal models;[30,31] 2) the potential to flush 'blocked' tubules (previously thought to be a significant pathogenic factor in ARF); 3) clinical reports of improved outcome,[32,33] and; 4) evidence of lower mortality in patients with polyuric ARF.[27,28-34] However, four prospective randomised controlled trials (PRCTs) of high-dose (3 - l0mg/kg) frusemide[28,35-37] have failed to demonstrate any

outcome benefit. These trials (numbering over 200 patients), revealed a similar incidence of dialysis (74% vs 79%) and mortality (55% vs 49%) between the frusemide and the placebo-control groups. If these small differences in outcome were clinically significant, it would require a multi-centre trial of over 600 patients to statistically remove any doubt of a type II error.

Table 1. Proposed renoprotective therapies

- Frusemide
- Dopamine
- Theophylline
- Mannitol
- Calcium channel blockers
- α_2 Adrenergic receptor agonists
- Cardiac glycosides
- Natriuretic peptides
- Prostaglandins
  - PGE_2
  - Prostacyclin
  - Mistoprostol
- Nitric oxide synthase inhibitors
  - L-NMMA
- Catecholamines
  - Adrenaline
  - Noradrenaline
  - Dobutamine
  - Dopexamine
- Intravascular volume loading
- Miscellaneous agents
  - Growth factors
    - Insulin-like growth factor 1
    - Epidermal growth factor
    - Hepatocyte growth factor
  - Bradykinin
  - Magnesium
  - Endothelin-1 antagonists
  - Low dose endothelin-1

Current data also suggests that high-dose frusemide does not benefit renal medullary oxygenation[10] and may exacerbate renal dysfunction, through the reduction in extracellular volume,[38] GFR,[39] and RBF.[10,40] To this must be added the common (although largely anecdotal) experience of many clinicians that persistent or uncontrolled use of this drug is a frequent cause of preventable ARF. Based on these data, support for high-dose frusemide has waned, although not entirely disappeared.

Interest in low-dose frusemide (e.g. 0.5 - 1 mg/kg) has been rekindled by evidence of its cytoprotective properties in animal models of ischaemic ARF[41-43] and evidence of improved medullary oxygenation.[10] Unfortunately there is also evidence that low-dose frusemide impairs autoregulation,[44] TGF,[45] and in the presence of hypovolaemia may redistribute blood flow towards the cortex not the medulla.[46] Its diuretic properties negate the utility of urine output monitoring, and polyuria may increase the risk of hypovolaemia.[37,38] In the light of these conflicting data it is not surprising that currently published clinical trials[38,47] (including one PRCT[48]) of low-dose frusemide in critically ill subjects do not support its use.

In summary, although low-dose frusemide may have in vitro cytoprotective properties, the routine use of frusemide as a renoprotective agent cannot be supported from current data. Persistent use of frusemide should be viewed with extreme caution in patients with other risk factors for ARF such as fluid restriction, diabetes, cardiac disease, or chronic renal impairment.

Dopamine

Dopamine is an endogenous diuretic and catecholamine that is active at α- and β-adrenergic and dopaminergic receptors. As a 'low-dose' infusion (e.g. 1 - 5 μg/kg/min) it has been advocated for decades as a promising renoprotective agent.[49] Its inotropic effects may improve cardiac output and renal perfusion pressure[37,50] whilst its intra-renal dopaminergic-1 receptor agonist properties reduce renal vascular resistance, proximal tubular Na^+ reabsorbtion[50] and improve medullary oxygenation in the presence of selective medullary vasoconstriction (e.g. cyclosporin and NSAIDs).[10,51] A number of ischaemic and nephrotoxic models of ARF support dopamine as a renoprotective agent[50] and there are numerous uncontrolled clinical reports of improved outcome in association with its use.

More recent studies, however, have thrown considerable doubt over the clinical role of low-dose dopamine. Renal vasodilatation does not necessarily occur in the compromised kidney[50,52] and its diuretic action increases urine output but not creatinine clearance.[53] Dopamine blunts TGF[54] and proximal Na^+ reabsorption, which opposes any beneficial effect on RBF and may explain the absence of any improvement in medullary oxygenation.[10,50]

Of the eighteen published clinical PRCTs not one has demonstrated improved outcome with low-dose dopamine. These trials have included critically ill patients,[53,55,56] postoperative cardiac,[57-59] vascular,[60-62] renal transplant,[63,64] liver transplant,[65] and general surgical[66] patients, and those exposed to various nephrotoxic insults.[67-71] Dopamine also harbours a number of unique and potentially serious side-effects including splanchnic ischaemia,[62,72-74] respiratory

depression,[75] neuroendocrine modulation of pituitary function,[76] and diuretic-induced hypovolaemia.[53]

In summary there are sufficient data to indicate that the routine use of low-dose dopamine has no place in the prevention or treatment of renal dysfunction.

Theophylline

Theophylline, a phosphodiesterase inhibitor and adenosine antagonist, increases urine flow by inhibiting proximal Na^+ reabsorption, and possibly by augmenting RBF resulting from its myocardial effect of increasing cardiac output. Some nephrotoxic[77,78] and ischaemic[79] ARF models support theophylline as a prophylactic agent, and adenosine antagonism may be beneficial in the presence of ischaemic renal vasoconstriction.[80] However, there are a number of theoretical disadvantages to theophylline.

The proximal diuretic action may increase the Na^+ load to the mTAL cells. Adenosine is not only a potent mediator of vasoconstriction in the ischaemic kidney[80] it is also a mediator of TGF[22] and the redistribution of cortical to medullary blood flow.[81] By blunting intra-renal protective mechanisms, non-selective adenosine antagonism may actually be counterproductive to tubular survival.

However, one prospective randomized controlled trial found that intravenous theophylline (5 mg/kg) given 45 minutes before the administration of intravenous radiographic contrast media, prevented a decrease in creatinine clearance[82], although another study using a low dose of theophylline failed to show any benefit in the prevention of contrast media induced nephrotoxicity.[83] The lack of sufficient clinical data precludes these drugs from routine use for renal protection.

Mannitol

Mannitol is an osmotic diuretic with anti-oxidant properties. It has been used widely as a prophylactic renal agent in the presence of crush injury,[84] renal transplantation,[85] and major surgery, as it has been shown to reduce total and medullary renal vascular resistance[86] and benefit a number of ischaemic[43,87,88] and nephrotoxic[85] models of ARF.

However, controlled clinical trials suggest that mannitol has little or no benefit in the setting of postoperative[89-91] or nephrotoxic[92,93] renal dysfunction. Elevation in GFR and inhibition of proximal Na^+ reabsorption will reverse oliguria, but can adversely effect the medullary oxygen supply:demand balance[10,94] and thus give the clinician a false sense of security.
Repeated use (e.g. for closed head injury) is nephrotoxic,[85] possibly due to renal vasoconstriction.[95] While there appears to be benefit in renal trans-plantation[96] there is no evidence to support its routine use in other critically ill patients at risk from renal dysfunction.

Calcium channel blockers

These drugs inhibit calcium (Ca^{2+}) ionophores in the cell membrane, and have diverse effects on cardio-vascular function. Calcium release is believed to play a significant role in tissue ischaemia-reperfusion injury and radiocontrast-induced renal vasoconstriction[77] and some studies have shown calcium channel inhibitors to be protective in animal models of ischaemic and nephrotoxic ARF.[97]

One PRCT of radiocontrast agents suggests that prophylactic nifedipine may prevent renal dysfunction in the presence of high osmolality agents.[98] High doses of Ca^{2+} antagonist have also been shown to be beneficial in renal transplantation.[99,100]

Unfortunately, there are no PRCTs to support its routine use in critically ill patients, and any renal benefit must be weighed against the cardiovascular side-effects associated with Ca^{2+} channel blockade.

α_2 Adrenergic receptor agonists

Clonidine is an α_2 receptor agonist which influences autonomic, haemodynamic and renal function. It has been shown to reduce sympathetic drive and increase urine flow,[101] providing prophylactic benefit in ischaemic[102] and nephrotoxic[103] models of ARF, and has been shown to improve early postoperative urine output and creatinine clearance in cardiac surgical patients.[104] However, further clinical trials are indicated for this intriguing drug before it can be recommended as a renal protective agent.

Cardiac glycosides

Cardiac glycosides inhibit the cellular membrane sodium- and potassium-activated adenosine tri-phosphatase (NaK-ATPase) and are primarily used for their inotropic and antiarrhythmic properties. In patients with cardiac failure, improved cardiac output may be beneficial in maintaining RBF. Because NaK-ATPase is also an essential component of tubular Na^+ reabsorption, cardiac glycosides may produce a natriuresis and reduce tubular metabolic demand. As a result they have been shown to be protective in an ischaemic model of ARF.[105] These drugs are also known for their cardiovascular side-effects and therefore their clinical benefits are limited.

Natriuretic peptides

Natriuretic peptides (e.g. atrial natriuretic peptide and urodilatin) are a group of endogenous atriopeptins which have natriuretic, diuretic and renoprotective

properties in animal models of ischaemic ARF.[106-108] Except for one small study in cardiac surgical patients,[109] controlled clinical trials do not support the use of urodilatin[110-111] or atrial natriuretic peptide as reno-protective agents.[108-112]

Prostaglandins

This group of endogenous mediators include the vasodilator prostaglandins (PGE_2 and prostacyclin) which are involved in renal autoregulation, TGF, and tubular cytoprotection.[16,113] Misoprostol (a synthetic vasodilator prostaglandin) is protective in ischaemic[43] and toxic[113] models of ARF. Prostaglandin inhibitors, such as NSAIDs, are known to exacerbate oliguria and medullary hypoxia,[10] and to be an independent risk factor for ARF. Clinical data on renal function and outcome are as yet unavailable, and the side-effects of systemic vasodilatation and hypotension may preclude their use as renoprotective agents.

Nitric oxide

Nitric oxide (NO) is an endogenous vasodilator of all vascular beds including the renal microvasculature. It has been shown to be an important modulator of renal vasodilatation, TGF, medullary Na^+ reabsorption and medullary oxygenation.[10,114] Inhibition of NO formation induces medullary hypoxia[115] and may be a mechanism for cyclosporin nephrotoxicity.[116] Intra-renal NO production has also been shown to increase GFR, produce a natriuresis and play a cytoprotective role in models of ischaemic and nephrotoxic ARF.[114]

However, NO is a systemic vasodilator that may adversely effect RBF. In an intriguing study using a hypotensive animal model, systemic NO inhibition (using the nitric oxide synthase inhibitor NG-monomethyl-L-arginine) was found not only to enhance blood pressure but also GFR,[117] underscoring the importance of defending renal perfusion pressure[19] over manipulation of intra-renal haemodynamics.

Catecholamines

Drugs in this class include endogenous (e.g. adrenaline, noradrenaline) and synthetic (e.g. dobutamine, dopexamine) catecholamines. These agents are used primarily to improve cardiac function (by enhancing the β_1-adrenergic inotropic and chronotropic activity) and support peripheral vascular function (by enhancing α_1-adrenergic pressor activity).

α_1-adrenergic receptor agonists were initially believed to be detrimental to renal function because an intrarenal bolus of noradrenaline has been used as an effective model of ischaemic ARF. However, this effect is the result of intense renal vasoconstriction that is probably dose and time dependent, and does not necessarily occur when these drugs are titrated at lower doses.

As autoregulation is impaired in critically ill patients, restoration and defence of renal perfusion pressure is considered to be important.[19] Adrenaline has been shown to produce a sustained increase in RBF in both a healthy and septic sheep model, even in the presence of systemic vasoconstriction and hypertension.[52] Low-dose dobutamine and dopexamine[118] have also been shown to be effective in improving creatinine clearance, presumably due to the result of improved systemic haemodynamics.[50,52] We have documented, using duplex Doppler techniques in a series of five stable critically ill patients, that an intravenous infusion of noradrenaline (1 - 16μg/min) sufficient to produce a dose-dependent rise in systemic vascular resistance and renal perfusion pressure (mean arterial pressure 80 - 120mmHg) also produced a relative rise in RBF and did not adversely effect renal vascular resistance or creatinine clearance. This is consistent with numerous published reports documenting the use of noradrenaline in critically ill patients, without apparent adverse renal effects.[56,73,119-122]

Intravascular volume loading

Intravascular fluid loading (e.g. intravenous isotonic saline) is the oldest, the most common, and probably the most reliable form of renal protection available. Persistent dehydration and hypovolaemia are common causes of renal impairment and ARF, particularly in the presence of other risk factors such as cardiac failure, diabetic nephropathy, chronic renal failure, and nephrotoxic insults. Volume loading improves cardiac output and blood pressure, induces renal vasodilatation,[86] increases RBF[123,124] and urine output,[124,125] in both animal and human subjects. Volume loading has also been shown to reduce the risk of renal impairment in the presence of renal ischaemia,[126] radiocontrast exposure,[10] and in post-operative subjects.[127,128]

The enormous significance of volume status is highlighted by the lengths to which this variable is controlled in animal and human models of ARF. As a result of its acknowledged importance it would now be impossible to design an ethically acceptable PRCT to assess the effect of volume status as a reversible cause of ARF.

The ideal resuscitation fluid is yet to be determined despite numerous comparative trials. This probably reflects the relative insignificance of fluid type in contrast to the importance of fluid resuscitation *per se*. Appropriate end-points for resuscitation are also difficult to define, especially in critically ill patients. The use of central venous and pulmonary artery

occlusion pressures have been shown to correlate poorly with volume status in critically ill subjects.[29] Once again the utility of urine output as a simple indicator of resuscitation cannot be under-estimated.

Although there are no PRCTs comparing the effect of pressor agents or volume loading on renal outcome, there are significant data to support the defence of extracellular volume, cardiac output, and perfusion pressure, in reducing renal damage and protecting renal function in patients at risk of acute renal failure.

Miscellaneous agents

Other endogenous agents with reported potential benefits to renal function include the growth factors[10,106,129] (e.g. insulin-like, epidermal-1, fibroblast, and hepatocyte, growth factors), bradykinins,[43] magnesium,[129] endothelin-1 antagonists,[130] and low dose endothelin-1 (which paradoxically produces medullary vasodilatation via NO induction[131]). The clinical benefits of these agents are unknown and await PRCTs.

Unfortunately, most agents either interfere with intra-renal protective mechanisms and urine output as a clinical guide to renal perfusion and medullary hypoxia. Much work remains to clearly identify the role of renoprotective agents, to develop clinically applicable models of ARF, and to develop reliable monitors of early renal dysfunction.

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