ABSTRACT

Introduction: The mortality of acute renal failure (ARF) is 50-80% in critically ill patients and has not fallen significantly despite numerous advances in critical care strategies and renal replacement technologies over several decades. (1) A major problem with conducting research into acute renal failure (ARF) is the lack of a consensus definition (2). More than 30 different definitions of ARF have been used in the literature. This lack of a common reference point created confusion and made comparisons difficult. The Acute Dialysis Initiative (ADQI) group of experts developed and published a consensus definition of ARF. This definition goes under the acronym of RIFLE. This definition classified the patients with renal dysfunction according to the degree of impairment into patient at risk (R), with injury (I), with failure (F), with sustained loss (L) and with end stage (E) status in relation to their renal function. (2) Rifle criteria were based on changes in the patients' glomerular filtration rate (GFR) and/or their urine output. (2)

Discussion: The prophylactic and therapeutic use of dopamine, the more studied vasoactive drug, actually has not been supported. For all other vasoactive drugs, at this moment, data available are contradictory and few conclusions can be made. To protect renal function, despite wide use of vasoactive drugs, only the maintenance of adequate volume replacement and perfusion pressure may be certainly recommended.

Conclusion: The use of vasoactive drugs is a pervasive practice in intensive care units, and hence, this area needs suitably powered, multi-center, randomized, placebo-controlled, double-blind studies to provide more rational indications for clinical practice.

KEY WORDS: intensive care unit, acute renal failure, renal protection, hemodynamic management, vasoactive drugs, renal replacement therapy

Introduction

The mortality of acute renal failure (ARF) is 50-80% in critically ill patients and has not fallen significantly despite numerous advances in critical care strategies and renal replacement technologies over several decades. (1) Postoperative ARF is the most common form of ARF in hospitalized patients and markedly increases perioperative morbidity and mortality. (1) The incidence of perioperative ARF varies with the type of surgery. Elective surgery has a lower risk compared to emergency surgery. (1) Multiple risk factors, including old age, chronic renal insufficiency, cardiac disease, sepsis, and concurrent use of nephrotoxic agents, such as radiocontrast dye and non-steroidal anti-inflammatory agents, influence the incidence of ARF in intensive care unit (ICU) patients. (1)
Renal vasoconstriction is also thought to play a role in the pathogenesis of septic ARF, along with hypovolemia and septic venedilation. (1) Patients with cardiogenic/vasodilatory shock, maintenance of adequate mean arterial pressure and cardiac output is fundamental for achieving adequate vital organ perfusion and function. (6) This treatment of hypotension or shock comprehends administration of fluid and vasoconstrictor drugs that may amplify renal ischemia and tubular injury. (6) Apart from fluid resuscitation, vasoactive drugs, such as dopamine, norepinephrine, epinephrine, and epinephrine, are often administered in shocked patients to improve either cardiac output or mean arterial pressure and to achieve optimization of organ perfusion and, therefore, renal perfusion. (7) With the exception of dopamine, there have been no randomized controlled trials of sufficient statistical power to detect differences in clinical outcome and degree of renal protection. (1) In critically ill patients, a continuous infusion of fenoldopam does not cause any clinically significant hemodynamic impairment and seems to be a new option in improving renal function, compared with renal dose dopamine. In early acute renal dysfunction, before severe renal failure has occurred, the attempt to reverse renal hypo-perfusion with fenoldopam is more effective than with low-dose dopamine. (8) Fenoldopam seems to play a role in preventing the progression to established acute renal failure or accelerating the recovery of renal function in critically ill patients. (8) Landoni et al, in a recent study, suggest that fenoldopam reduces mortality and the need for renal replacement therapy in patients with acute renal injury. (9) It is still unclear what hemodynamic manipulation is appropriate to obtain renal protection and ameliorate renal perfusion. (7) Most intensive care unit patients receive continuous infusion of two or more vasoactive drugs at the same time. In intensive care unit patients, the main goal is to maintain organ perfusion by firstly, attempting a fluid challenge and secondly, administering drugs. The most commonly used drugs in ICU are vasoconstrictors and/or vasodilators including different inotropic drugs such as norepinephrine, epinephrine, dobutamine, levosimendan and dopamine. Actually, the question is whether non-pharmacological strategies are more effective than drugs in preventing acute renal failure or progression of renal damage? (10)

Cardiovascular drugs and the kidney in ICU

In clinical practice, after an adequate preload index has been achieved with volume loading, a loop diuretic is started to increase urine output. Although most clinical studies report an effective increase in urine output, the evidence for a beneficial effect of loop diuretics on renal function is limited. It is probable that the patients who respond to loop diuretics are characterized by a less severe form of renal failure. (11) Other clinical studies show a deleterious effect of loop diuretics on renal function. (11) None of these studies have statistical power. An explanation may be an excessive pre-load reduction with renal vasoconstriction due to activation of the renin-angiotensin system and sympathetic stimulation, on the other hand, loop diuretics induced diuresis relies only on decreased reabsorption in non-obstructed tubuli, whereas tubular obstruction is not prevented or remedied. (11) Also the final effect of loop diuretics on renal blood flow is the resultant of several partially opposing effects and the net effect is difficult to predict. (11)

In the same manner mannitol has also been used for renal protection. The osmotic diuresis may induce volume depletion and increased distal solute delivery may increase medullary oxygen consumption. Mannitol has been shown to induce apoptosis in endothelial and epithelial cells, and high doses can induce acute renal failure too. (11) For this reason mannitol has not been proven to be a value for renal protection. (11) Dopamine was the first drug used in ICUs. The first clinical description of
its use was in patients with congestive heart failure (12). Dopamine acts on two populations of dopamine receptors, DA1 and DA2, located on cells in vascular smooth muscle of the renal, mesenteric, coronary, cerebral, gastric and hepatic arteries. The binding of dopamine to these receptors results in localized arterial vasodilatation, increase in glomerular filtration rate, renal blood flow and sodium excretion. At higher doses dopamine stimulates dopaminergic and adrenergic receptors, such as β receptors (3-5 microgram/Kg/min) and α receptors (above 5 microgram/Kg/min), with inotropic and vasoconstrictor action. The use of low dose dopamine (1-3 mcg/kg/min) was widely accepted in common clinical practice in an attempt to prevent or to treat renal dysfunction. A systematic review of 58 studies concludes that there is no evidence, despite its widespread use, to support the use of low dose dopamine to prevent or to treat ARF. (14)

The improvement in urine output, of non-shocked patients, is only an expression of the diuretic effect of dopamine rather than its protective effect on renal function. (15) Furthermore, this diuretic effect wanes by 48 hours after the start of a continuous infusion. (16) Despite this, in oliguric patients dopamine failed to reverse oliguria or hypotension, and did not significantly modify clearance of creatinine, incidence of acute renal failure, need for dialysis or patient survival. (17) Particularly in critical patients, dopamine has some potential disadvantages, like an earlier onset of gut ischemia, tissue necrosis and digital gangrene. A meta-analysis by Kellum et al. excluded any effect of dopamine on the risk of ARF or mortality, although dopamine was totally inefficient in preventing or treating renal dysfunction. (14) The only dopamine effect that has been confirmed is the temporarily increase in glomerular filtration rate in septic shock patients due to a reverse in vasoconstriction action of vasopressor drugs used in these patients (18). The natriuretic effect of dopamine increases solute delivery to the distal tubular cells, which may increase medullar oxygen consumption and exacerbate the ischemia during hypotension. This effect could explain why increases in renal blood flow are not protective. (7)

The ANZIC study analyzed the use of dopamine in 324 critically ill patients with systemic inflammatory response syndrome and oliguria, and confirmed that there are no differences in mortality, ARF, requirement of renal replacement therapy, length of hospital stay or peak serum creatinine. (18) Renal dose dopamine may increase the risk of postoperative atrial fibrillation, especially in critically ill patients, where impaired renal clearance of dopamine results in high plasma levels that stimulate postsynaptic dopaminergic 2 receptors. (19) A dopamine infusion results in a rapid ventricular response and hemodynamic instability due to an increase in the atrio-ventricular conduction rate. (20) "Low dose" dopamine can worsen renal perfusion in patients with acute renal failure, which adds to the rationale for abandoning the routine use of "low-dose" dopamine in critically ill patients. (21) Although norepinephrine is a very common drug used in septic shock patients, norepinephrine has only a moderate β1 and β2-adrenergic effect but a strong α-adrenergic effect, that causes vasoconstriction in all vascular beds. The postsynaptic alpha 1 receptor activity sustains arterial blood pressure and peripheral vascular resistance but inducing vasoconstriction can compromise renal, splanchnic and mesenteric blood flow. Dopamine may counteract the norepinephrine-induced decrease in renal blood flow in healthy volunteers. (13) Actually there are insufficient data to define the effect on the kidney, either in normal subjects or under septic conditions. (7) The restoration of adequate blood pressure using norepinephrine is associated with increased urine output, but this is achieved with any other drug that also improves blood pressure, and probably also renal blood flow and glomerular filtration rate. (7) There are no reasons to avoid norepinephrine administration because of concerns that it would have a specific adverse effect on renal function. When compared to high dose dopamine, norepinephrine is more effective in restoring mean arterial pressure. For this reason it is the vasopressor of choice in vasodilated hypotensive states with preserved or increase cardiac output. (7) Norepinephrine was more effective in restoring normotension in 32 patients with hyperkinetic and hypotensive septic shock to high dose dopamine. (22) There are no controlled data to define the effects of norepinephrine on the kidney in the clinical contest. However, many patients’ series have not been published. Clinical experience in septic patients and cardiac patients with inflammatory or pharmacological vasodilation is also positive. At this time, there is no reason to fear the effects of norepinephrine. If it is used to support a vasodilated patient, after adequate intravascular filling has occurred and after a normal or increased cardiac output has been established, it is likely to be a friend and not a foe. (23)

In ICU patients some other drugs are use less frequently to maintain adequate mean arterial pressure. Phényléphrine, a predominant α adrenergic receptor-mediated agonist, increases blood pressure mainly by increasing systemic vascular resistance. In septic patients it appears not to have an adverse effect on the kidney and shows a stable serum creatinine concentration and increase in urine output. (7) The same effects are noted in post-operative patients with cardiopulmonary bypass. (7) Recently, vasopressin has been proposed as an alternative to catecholamine for persistent hypotension in septic shock. In catecholamine hypo-responsive patients, peripheral vessels respond surprisingly well to intravenous injections of vasopressin. (24)
In healthy patients, vasopressin has minimal effect on vascular tone, despite successfully restoring blood pressure in vasodilating conditions, like septic shock or hepatorenal syndrome. Vasopressin acts via three types of receptors: V1a receptor, located on vascular smooth muscle cells, mediates vasoconstriction; V2 receptor, mainly located on the distal convoluted tubules and medullary collecting ducts of the kidney, mediates water movements, and V3 receptor, mainly located in the anterior hypophysis, is involved in the control of corticotrophin release. In addition, vasopressin is capable of closing activated ATP-sensitive potassium channels. In a septic model, organ blood flow through the left ventricle, right ventricle, ventricular septum, kidney, liver, spleen and skeletal muscle was measured using radioisotope tagged micro spheres in two groups of patients treated with vasopressin or norepinephrine. Vasopressin increased renal blood flow and decreased hepatic arterial blood flow, whereas, norepinephrine did not. A multicentric, open-label randomized trial in early hyperdynamic septic shock found that high-doses of vasopressin, used as a single vasopressor agent, initially failed to maintain the mean arterial pressure above 70 mmHg which was the first topic of this trial.

Terlipressin is the drug of choice in hepatorenal syndrome in 50% of patients, and appears safe and well tolerated. Terlipressin, in a randomized study, was compared to norepinephrine looking at the effects on creatinine clearance and urine flow in septic patients and the authors concluded that renal function is improved with both drugs. Morelli et al. has previously demonstrated that terlipressin decreases oxygen consumption, although the measurements were not performed independent of cardiac output. Since it has been speculated that terlipressin might exhibit anti-inflammatory effects that decrease oxygen demand of the tissues, the reduction of oxygen consumption may be interpreted as a positive consequence of terlipressin action.

When other drugs fail to raise mean arterial pressure, use of epinephrine may be necessary. Epinephrine acts simultaneously on α- and β-receptors. At low doses it has β-adrenergic effects and increases cardiac output. At higher doses, its α-adrenergic effect causes vasoconstriction, particularly in the splanchnic and renal vascular bed, and results in elevated systemic vascular resistances and blood pressure. One of the most important uses of epinephrine in the ICU is in septic shock and besides this, in cardiopulmonary resuscitation.

Epinephrine infusion is associated with a significant increase in renal vascular resistance and decrease in renal blood flow. Absolute RBF index and renal oxygen consumption, creatinine clearance and urine output remained constant. Epinephrine, despite an increase in mean arterial pressure, may cause undeliverable splanchnic effects on ICU patients such as lower splanchnic flow and oxygen uptake, lower mucosal pH and higher hepatic vein lactates. We have very limited data about the renal effects of epinephrine compared with placebo or other vasoactive drugs. Actually, data available on the renal effects of epinephrine are of a level III or IV evidence or animal study, and knowledge about the renal effects of epinephrine is still limited.

In the late phase of septic shock, the cause of hypotension is vasodilation and cardiac failure with low cardiac output. In this phase, the use of inotropic drugs is necessary to maintain organ perfusion. Dobutamine is the drug of choice in the case of acute heart failure or in shock with low cardiac output. In ICU patients, the association between norepinephrine and dobutamine is most frequently seen in septic shock patients to maintain mean arterial pressure and tissue perfusion. Dobutamine is a partial agonist towards β1- and β2-adrenergic receptors with little effect on α-adrenergic receptors and increases heart rate, cardiac index and oxygen delivery within a therapeutic range of 1 to 20 mcg/Kg/min. The inotropic and chronotropic actions of dobutamine are associated with therapy-derived tachycardia, which would bear the potential for increasing myocardial oxygen consumption and ischemic injury. In normovolemic patients, dobutamine increases cardiac index with no change or increase in systemic blood pressure. In hypovolemic patients, the use of dobutamine may induce reduction in mean arterial pressure (β2 effect) and increase in oxygen consumption because of potent vasodilatation through activation of β adrenergic receptors. The specific renal effect is probably due to its ability to increase cardiac output. The additive effect of cardiac α1 and β1 agonist activity gives dobutamine a strong cardiac inotropic action. In critically ill patients, dobutamine is rarely used as a single agent because of the vasodilatory β2 effect, and then it is difficult to assess the effect of this drug alone on the kidney.

The increase in cardiac output and consequent increase in renal blood flow have a beneficial effect on renal function, but there is insufficient data to recommend its use for renal protection.

Dopexamine also increases splanchnic and renal perfusion, via a dopaminergic effect. Dopexamine has marked intrinsic agonist activity on β2 adrenergic receptors and weak agonist activity on DA1 and DA2 dopaminergic and β1 adrenergic receptors. A total of 351 articles were analyzed in a systematic review of which 3 articles investigated the effect of dopexamine on renal function in elective high risk surgery and 1 of these investigated renal perfusion in critically ill patients. Despite some authors suggesting that dopexamine may protect renal function in patients undergoing cardiac surgery, there is no evidence to suggest a protective role in critically ill patients. Some protective effects may be attributable to a vasodilating action that may unmask a covert hypovolemia, necessitating the use of additional volume expansion. The fluid excess received by the patient may explain some beneficial effects attributed to dopexamine.
Nitr**oglycerine** is a potent dilator on vascular smooth muscle, because it inhibits vascular smooth muscle contraction by increasing cGMP. (40) Nitr**oglycerine** produces venodilation at very low dosages, with little additional vasodilatation of the venous circulation with increasing doses. Nitrates increase arterial diameter and improve arterial conductance, and at higher doses produce dilation of the arteriolar or resistance vessels of the body. (41) Despite this, renal blood flow remains essentially unchanged or barely decreases after nitroglycerin infusion, although reflex sympathetic activity may cause secondary vasoconstriction. (41) This failure of systemic administration of nitroglycerin to increase renal blood flow has previously been demonstrated in both animals and humans with heart failure. These findings indicate a selective vasodilatory effect of nitroglycerin on renal conductance but not on resistance blood vessels. (42) During infusion of nitroglycerin in patients with chronic heart failure renal sympathetic activity decreases in spite of a reduction in arterial pressure and cardiac filling pressure. This phenomenon is not observed in healthy volunteers. (42) The attenuation of renal sympathetic responses contributes to the beneficial effect of nitroglycerin in chronic heart failure patients. (42) Sodium nitro**prusside is** a peripheral vasodilator, acting directly as arterial and venous smooth muscle relaxant, like nitroglycerin. (43) Its metabolism leads to cyanmethemoglobin formation and free cyanide ions. From a renal point of view it increases renin release and contributes to over activity of the sympathetic nervous system, that causes vasoconstriction and reduction in renal blood flow. (43) Many authors are studying the use of a new drug, fenoldopam, in preventing renal damage in high-risk patients in the ICU or during the perioperative period. Fenoldopam is a selective dopamine receptor-1 (DA-1) agonist that, at low doses (0.06-0.1 mcg/Kg/min), causes DA-1 receptor mediated vasodilatation, preferentially at afferent arterioles and then reduces renal vascular resistances and improves renal blood flow, fractional excretion of sodium and free water clearance. (7) Fenoldopam is a six times more effective renal vasodilator than dopamine and does not activate other adrenergic receptors. At doses of 0.1 mcg/Kg/min no significant decrease in systolic blood pressure was observed, whereas, at higher doses, fenoldopam is a potent vasodilator. (43) In renal transplant patients there seem to be no differences in the dopamine versus the fenoldopam group, probably because these two drugs do not work on denervated kidney or the two groups are too small to explain statistical differences. In fact, the authors report a superior trend in urine output, serum creatinine and renal vascular resistance in the fenoldopam group undergoing elective aortic surgery or cardiopulmonary bypass. (44) Moreover, fenoldopam seems to preserve renal function counterbalancing the renal vasoconstrictive effects of cyclosporine in kidney (45) and liver (46,47) transplant patients. It is not clear if this promising effect would lead to a reduction in morbidity and mortality rate and hence, in the cost of medical care. (48)

**The kidney in ICU**

For acute renal failure, hemodialysis currently offers two options: intermittent hemodialysis (IHD), whereby relatively short dialysis sessions are performed every day or every other day, and continuous renal replacement therapies (CRRT), which are performed continuously. (49) Recently, low efficient daily dialysis (SLEDD) was introduced as a third possibility. This alternative method combines the advantages of CRRT with those of IHD. CRRT has some theoretical advantages to maintain hemodynamic stability that is related to the recovery of renal function, correction of metabolic acidosis and malnutrition, removal of cytokines and solute. CRRT also has some disadvantages. In fact CRRT needs continuous anticoagulation therapy and the necessary immobilization for
Continuous renal replacement therapies (CRRT) allow extracorporeal treatment in critically ill patients with hypercatabolism and fluid overload. CRRT have commonly used three types of depurative mechanisms: convection, diffusion and adsorption by the filtering membrane. (50)

Acute Dialysis Quality Initiative (ADQI) in 2002 has defined some criteria to start CRRT in clinical practice.

- Anuria - Oliguria (diuresis ≤ 200 ml in 12 h)
- Severe metabolic acidosis (pH < 7.10)
- Hyperkalemia (BUN ≥ 80 mg/100 ml)
- Hyperkalemia (K+ ≥ 6.5 mEq/L)
- Clinical signs of uremic toxicity
- Severe dysnatremia (Na + ≤ 115 o ≥ 160 mEq/L)
- Hyperthermia
- Anasarcha or severe fluid overload
- Multiple Organ Failure including renal dysfunction
- SIRS, Sepsis or Septic shock with renal dysfunction

In septic patients CRRT may remove non-selective pro and anti-inflammatory mediators. The treatment dose in CRRT is a major factor concerning survival in acute renal failure in the critically ill patient. (50) Despite this, there is accumulating evidence of increased efficacy of high-volume hemofiltration compared to conventional continuous veno-venous hemofiltration in terms of laboratory and clinical improvement, including survival, the evidence is still not strong to suggest high-volume hemofiltration outside clinical studies. (50)

Acute renal failure is increasingly seen as part of multiple organ dysfunction syndrome (MODS) in critically ill patients. Severe sepsis and septic shock are primary causes of MODS. CRRT may remove bacterial lipopolysaccharides and other inflammatory mediators. (50) Drugs significantly eliminated by the kidney are likely to experience substantial removal during CRRT, and a supplemental dose corresponding to the amount of drug removed should be administered. (51) In this case, it is mandatory to monitor plasma concentrations to maintain adequate plasma concentrations. (51)

Other blood purification techniques using large-pore membranes or plasma filtration with adsorbent perfusion are in the early stages of clinical testing. (50) Also in ICU patients, radio-contrast nephropathy (RCN) is another cause of acute renal failure. The incidence of radio-contrast nephropathy is 50% or more in high-risk patients, particularly those with underlying chronic kidney disease, diabetes mellitus or severe heart failure. In these patients, prophylactic strategies should be used to reduce the risk of renal injury. The prevention of renal injury may include the limitation of radio-contrast dose, the discontinuation of non-selective NSAIDs or selective COH-2 for 24-48 hours prior to and following the procedure. (48) Intravenous isotonic saline solutions should be administered and in addition loop diuretics should be held prior to contrast administration.

The benefit associated with the administration of N-acetylcysteine remains debatable, but this drug has minimal toxicity and is inexpensive. (48) The use of N-acetylcysteine should not, however, provide a false sense of protection. Mannitol, dopamine and fenoldopam have been shown to be ineffective and in some case deleterious and should not be used. Monitoring renal function following the administration of iodinated radio-contrast is also important in the first 24-48 hours.

If necessary, renal replacement therapy may be used to rapidly remove the radio-contrast. This is one of the indications for renal replacement therapy in the last 20 years.

**Conclusion**

The prophylactic and therapeutic use of dopamine, the more studied vasoactive drug, has not actually been supported. For all other vasoactive drugs, at this moment, data available are contradictory and few conclusions can be reached. To protect renal function, despite wide use of vasoactive drugs, only the maintenance of adequate volume replacement and perfusion pressure may be certainly recommended. The use of new interesting vasoactive drugs is still a pervasive practice in the intensive care unit, but this area needs suitably powered, multicentric, randomized, placebo-controlled, double-blind studies to provide a more rational approach to clinical practice or to confirm all the preliminary data.

**REFERENCES**


