Editorial

Renal failure in cardiac surgery: in search of the golden bullet

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It is difficult to determine the true incidence of peri-operative acute kidney injury (AKI). Due to its heterogeneous nature and multifactorial aetiology, the reported incidence varies widely depending on the definition used and population studied [1]. Cardiac surgery is a well-known risk factor for the development of AKI; the incidence of AKI may be as high as 40% during the peri-operative period [2], with up to 5% of patients subsequently requiring ongoing renal replacement therapy [3,4]. Patients who develop AKI have higher rates of mortality, as well as greater resource requirements, adding a significant financial burden to healthcare systems [5]. There are numerous reasons for this high incidence including: a high-risk population; the effects of the cardiopulmonary bypass period; and cardiovascular instability with vasoplegia that often develops during or after cardiopulmonary bypass. Confronting vasoplegia with vasoconstrictors may not be sufficient, at times requiring unorthodox measures including administration of vitamins C, B12, methylene blue and steroids. The exact mechanism of AKI related to cardiac surgery is unknown, but it is likely to be multifactorial with haemodynamic instability, oxidative stress, ischaemia, micro-emboli and nephrotoxins all contributing to renal cell injury. The development of AKI following cardiac surgery can be particularly detrimental with effects of AKI such as hyperkalaemia, acidosis and fluid overload being harmful for hearts recovering from ischaemic-reperfusion injury.

Risk factors

Over the years, several studies have examined risk factors and prognostic markers for developing AKI after cardiac surgery and whether these can be modified with effect. This work has primarily taken the form of attempting to define an 'at-risk' group both with readily available information (e.g. oliguria, pre-operative renal function and diabetes) and more novel biomarkers, including interleukin-18, insulin-like growth factor binding protein-7 and neutrophil gelatinase-associated lipocalin. This information is usually amalgamated into a scoring system such as the Cleveland Clinic system, aiming to identify those patients at high risk of AKI post cardiac surgery [6]. Newer models include further information such as aortic cross-clamp time and pre-operative cystatin-C [7], variables which may improve the accuracy of the score but limits its utility as a pre-operative screening tool. The question that then arises, having identified the high-risk group, is how to reduce this risk? Research on specific interventions has included work on the use of N-acetyl cysteine [8,9], sildenafil [10], forced diuresis [11], remote ischaemic preconditioning as well as volatile agents, all with limited, little or no success [12].

Identification of patients at risk of postoperative AKI is important, but perhaps more important is early recognition and treatment of postoperative hypotension and organ hypoperfusion. It has been

hypothesised for years that one of the main mechanisms of injury is renal hypoperfusion. Studies have been performed trying to reduce hypoperfusion with higher limits for mean arterial pressure during cardiopulmonary bypass, but with little effect [13]. Despite this, Ngu et al. recently showed that hypotension post-cardiopulmonary bypass for an extended time-period is associated with an increased risk of de-novo postoperative renal replacement therapy [14]. They found that mean arterial pressure < 65 mmHg for over 10 min postoperatively was associated with renal replacement therapy with an adjusted odds ratio of 1.12 (95%CI 1.06–1.18). However, this association appeared weaker when compared with other factors such as heart failure, emergency surgery and postoperative atrial fibrillation. Despite the widespread recognition of peri-operative AKI and its sequelae, the identification of an efficacious preventative or therapeutic strategy has been elusive. Consequently, it is clear that thinking of AKI as merely a single organ injury is too simplistic. Instead, it should be recognised as a systemic disease process that can provoke remote organ dysfunction, including cardiac, pulmonary, neurologic, hepatic, gastrointestinal and immunological dysfunction [1].

Angiotensin-2

In a recent issue of the journal, Coulson et al. reported the initial findings of their feasibility study on the use of angiotensin-2 infusion during and after cardiac surgery to reduce the incidence of AKI [15]. They hypothesised that AKI is at least in part due to hypotension and renal hypoperfusion. The combined action of angiotensin-2 as a potent systemic vasoconstrictor and its direct effects on the kidneys could mean it is a viable alternative or addition to the vasopressors used commonly in preventing postoperative organ hypoperfusion.

The additional effects of angiotensin-2, rather than simply its action as a vasopressor, may make this molecule a more promising development than previous agents. As well as leading to the contraction of smooth muscle producing vasoconstriction, angiotensin-2 also causes renal tubular sodium, chloride and water retention, increasing the effective circulating volume, as well as increasing perfusion of the glomerular apparatus. This renal specific action may, in theory, provide an additional benefit in the prevention of postoperative AKI. Coulson et al. demonstrated the feasibility of performing a randomised controlled trial comparing angiotensin-2 and noradrenaline; future work will need to assess if the theoretical advantage of angiotensin-2 in this high-risk group is correct.

Yet whilst this study provides further insights into the management of these patients, whether it will lead to improved outcomes remains questionable. Despite knowledge of the risk factors for

development of AKI, there has been no reduction in the incidence of the disease over the past 20 years and specific renal protection and treatment strategies have not shown any benefit. It may be the case that the damage is already done secondary to the inflammatory effects of cardiopulmonary bypass and the surgery itself causing tissue damage, with hypotension being a marker of this damage rather than the primary cause of hypoperfusion [16]. Maintaining blood pressure postoperatively may help to prevent secondary renal injury but we may never be able to prevent AKI in some patients. It is difficult, therefore, to see how the choice of vasopressor could affect the outcome if the target blood pressure is met.

Personalised care

In the last decade, research and clinical focus have been directed towards more personalised health care management; for example, monitoring of cerebral autoregulation in determining the optimal relationship between cerebral blood flow and mean arterial pressure in patients undergoing cardiac surgery. This dynamic relationship may fluctuate substantially intra-operatively and postoperatively in intensive care, negating the simple acceptance of a numeric mean arterial pressure value that may theoretically be acceptable as a sufficient value for a particular patient [17]. Adhering to maintaining cerebral autoregulation during surgery may reduce the incidence of central nervous system complications [18]. Similar principles may be applied to renal perfusion pressure by attaining optimal mean arterial pressure for the individual patient, particularly in patients with pre-existing renal injury. This approach will require further testing via interventional trials; however, patients with even mild pre-existing renal insufficiency may benefit most from these interventions [19].

Another current research strategy to prevent AKI after cardiac surgery involves the peri-operative use of α-2 agonists, particularly dexmedetomidine, due to their anti-inflammatory and anti-apoptotic effects [20]. A recent meta-analysis of randomised controlled trials showed protective effects of dexmedetomidine in reducing the incidence of AKI after cardiac surgery [21]. Alpha-2 agonists are a unique class of drugs that have numerous useful effects including analgesia, anxiolysis, sedation and anaesthesia sparing effects.

Alpha-2 agonists selectively bind to pre-synaptic α-2 adrenergic receptors located in the central nervous system (specifically the brain stem and locus coeruleus) to activate a negative feedback mechanism that inhibits central sympathetic outflow with a resulting decrease in systemic adrenaline and noradrenaline production [22]. This inhibition of central sympathetic outflow

attenuates peri-operative haemodynamic abnormalities and the surgical stress response, mitigating some of the mechanisms that can lead to peri-operative renal injury [23,24].

Alpha-2 adrenoreceptors are distributed widely within the renal proximal and distal tubules and peri-tubular vasculature. Local responses to α-2 adrenoceptor activation in the kidney are vasodilation, inhibition of antidiuretic hormone and renin release leading to increased renal blood flow, increased glomerular filtration rate and increased secretion of sodium and water. Rodent studies have shown that α-2 adrenoceptor agonists stimulate urine flow and enhance renal function likely through the modulation of vasoreactivity [25]. Due to these novel actions, the use of α-2 agonists is now being explored for prevention of peri-operative acute kidney injury. However, despite these potential benefits, the use of α-2 agonists may be limited by clinically significant haemodynamic adverse effects such as hypotension and bradycardia [23].

The use of pulsatile cardiopulmonary bypass has been mooted previously with mixed results with relation to AKI prevention. Pulsatile flow, as opposed to continuous flow, is hypothesised to reduce the inflammatory response related to cardiopulmonary bypass and improve microvascular flow, thereby reducing end organ damage. A small prospective study showed that pulsatile bypass maintained creatinine clearance whereas non-pulsatile bypass resulted in a reduced postoperative creatinine clearance in elderly patients undergoing aortic valve replacement [26]. However, a much larger retrospective study of over 2000 patients demonstrated no difference in renal function with pulsatile and non-pulsatile cardiopulmonary bypass. There was also no difference in secondary outcomes such as length of hospital stay or mortality [27].

Appropriate peri-operative blood management may reduce the risk of AKI by ensuring adequate perfusion and oxygenation to the kidneys. Anaemia, which is present in up to 30% of patients presenting electively for cardiac surgery in the UK, is well-established as a risk factor for developing AKI [28]. Given this, prevention of anaemia with pre-operative intravenous iron may seem an obvious way to reduce the risk of AKI. However, pre-operative anaemia management has not yet been conclusively proven to raise the haemoglobin in any significant way, let alone to be of benefit in reducing AKI [29]. Intra-operatively, the combination of cardiopulmonary bypass, high dose anticoagulation and the nature of the surgery itself predispose cardiac patients to a high risk of blood loss and subsequent transfusion. However, blood transfusion itself is not uncomplicated and there is some evidence that it may also increase the risk of AKI post cardiac surgery [30].

Drug regimens

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are beneficial for the long term survival of patients with heart failure, post myocardial infarction and chronic kidney disease [31]. However, continuing angiotensin-converting enzyme inhibitors/angiotensin receptor blockers pre-operatively is associated with an increased incidence of intra-operative hypotension, although with no change in mortality [32]. The prevalence of intra-operative hypotension is reflected in non-cardiac surgery international guidelines which recommend the pre-operative discontinuation of these drugs [33]. In cardiac surgery, where peri-operative hypotension may be more severe due to the additional stress and inflammatory effects of cardiopulmonary bypass, there may be even more reason to withhold these drugs pre-operatively [34]. However, the recommendations specific to cardiac surgery are based on limited evidence and more research is required in this area.

Avoidance of nephrotoxins in the context of patients at elevated risk of developing an AKI is obvious. However, the existence of contrast nepthropathy remains controversial. It is not within the scope of this editorial to finally answer this question but the evidence seems to suggest that in patients with normal or mildly impaired renal function there is very low risk of developing contrast-induced nephropathy [35]. For patients with already impaired renal function it is difficult to tease apart whether contrast plays a role in the worsening of their renal function or if the developing pathophysiology behind the need for contrast computed tomography or angiographic procedures is actually the cause [35]. If a patient requires imaging or angiographic procedures after cardiac surgery, it seems pertinent to use the lowest possible dose of contrast with expert guidance from radiologists.

Fluid management is important in both renal and cardiac disease, but often with conflicting aims. Peri-operative goal-directed therapy is another controversial area aiming to address this balance. Discussion exists as to which ‘goals’, if any, to target in the peri-operative period. The routine use of transoesophageal echocardiography intra-operatively, and the postoperative use of pulmonary artery catheters where appropriate, provides useful information regarding patients’ volume status and cardiac output. A systematic review and meta-analysis demonstrated that goal-directed therapy improved post cardiac surgery complications but not overall mortality, with the caveat that the analysis included only small studies with large heterogeneity [36].

Acute kidney injury in cardiac surgery is a common and serious complication with a complex pathophysiological basis. In our opinion, it is unlikely that the use of one single drug, be it

angiotensin-2 or another, will drastically reduce its incidence. However, the feasibility trial performed by Coulson et al. paves the way forward for future studies to assess this possible reno-protective drug in a multi-modal pathway. Until then, the mainstays of preventing AKI in cardiac surgery must remain the pre-operative risk assessment of acute and chronic comorbidities; discontinuation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; avoidance of nephrotoxins; intra-operative goal-directed therapies including targeted individualised mean arterial pressure; optimising oxygen delivery to the kidneys via treatment of anaemia; and, postoperatively, strict adherence to reno-protective bundles.

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