Author/s:
Lankadeva, YR;May, CN;Bellomo, R;Evans, RG

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REVIEW ARTICLE

Role of perioperative hypotension in postoperative acute kidney injury: a narrative review

Yugeesh R. Lankadeva[1,2,*], Clive N. May[1,2], Rinaldo Bellomo[2] and Roger G. Evans[1,3]

[1]Pre-clinical Critical Care Unit, Florey Institute of Neuroscience and Mental Health, Australia, [2]Department of Critical Care, Melbourne Medical School, University of Melbourne, Melbourne, VIC, Australia and [3]Cardiovascular Disease Program, Biomedicine Discovery Institute and Department of Physiology, Monash University, Melbourne, VIC, Australia

*Corresponding author. E-mail: yugeesh.lankadeva@florey.edu.au

Summary

Perioperative hypotension is common and associated with poor outcomes, including acute kidney injury (AKI). The mechanistic link between perioperative hypotension and AKI is at least partly a consequence of the susceptibility of the kidney, and particularly the renal medulla, to ischaemia and hypoxia. Several critical gaps in our knowledge lead to uncertainty about when and how to intervene to prevent AKI attributable to perioperative hypotension. First, although we know that the risk of AKI varies with both the severity and duration of hypotensive episodes, 'safe' levels of arterial pressure have not been identified. Second, there have been few adequately powered clinical trials of interventions to avoid perioperative hypotension. Thus, most evidence surrounding perioperative hypotension is observational rather than based on randomised clinical trials. This means that the link between perioperative hypotension and AKI may represent association (where both phenomena reflect illness severity) rather than causation. Third, there is little information regarding the relative risks and benefits of various clinically available therapies (e.g. vasoconstrictors, i.v. fluids, or both) to treat and prevent perioperative hypotension, particularly with regard to renal medullary perfusion and oxygenation. Fourth, there are currently no validated, clinically feasible methods for real-time clinical monitoring of renal perfusion or oxygenation. Thus, future developments in perioperative kidney-protective strategies must rely on the development of methods to better monitor renal perfusion and oxygenation in the perioperative period, and thereby guide timing, intensity, type, and duration of interventions.

Keywords: acute kidney injury; autoregulation; renal circulation; renal hypoxia; renal medulla; vasopressor

Editor's key points

- Perioperative hypotension is associated with acute kidney injury (AKI). There is some evidence that avoidance of intraoperative hypotension reduces AKI, but uncertainty remains as to what level of arterial pressure to avoid and which treatments of perioperative hypotension are most kidney-protective.
- In this narrative review, the authors identify mechanisms that render the kidney susceptible to ischaemia and hypoxia during perioperative hypotension and summarise what is known about the effects of treatments for hypotension on renal medullary perfusion and oxygenation.

Worldwide, more than 300 million surgical procedures are performed annually,[1] including around 2 million cardiac surgical procedures.[2] The incidence of acute kidney injury (AKI) after noncardiac surgery varies according to the procedure itself, with estimates from 2.9% to 57.4%.[3] Approximately 0.3% of patients require postoperative dialysis.[4] AKI is also a major

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Table 1 Perioperative hypotension and its association with acute kidney injury. AKI, acute kidney injury; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass. The relevant surgical epoch (preoperative, intraoperative, and postoperative, or before, during, and after CPB) is in bold italic.

Authors	Setting	Definition of hypotension/intervention	Findings in relation to AKI
Noncardiac surgery			
Primary publications (observational)		Definition of hypotension	
Walsh and colleagues[26] (2013)	Retrospective cohort; single centre; *n*=18 989 surgical procedures	Intraoperative MAP <75, 70, 65, 60, or 55 mm Hg	Risk of AKI was associated with both severity and duration of ***intraoperative*** hypotension, but it increased substantially at MAP <55 mm Hg
Sun and colleagues[27] (2015)	Retrospective cohort; single centre; *n*=5127 patients	Intraoperative MAP <65, 60, or 55 mm Hg	Risk of AKI was associated with both severity and duration of ***intraoperative*** hypotension
Saito and colleagues[28] (2016)	Retrospective, single-centre cohort of 76 vasopressor-dependent patients who had undergone cardiovascular surgery	Time-weighted averages of arterial pressure, central venous pressure, and perfusion pressure in the ICU relative to pre-morbid baseline values (continuous variables)	Patients with AKI progression had relative deficits in ***postoperative*** diastolic arterial pressure and both mean and diastolic perfusion pressure
Salmasi and colleagues[29] (2017)	Retrospective cohort; single centre; *n*=57 315 patients	Intraoperative MAP <75, 70, 65, 60, or 55 mm Hg, or >10, 15, 20, 25, or 30% below baseline	Risk of AKI was associated with both severity and duration of ***intraoperative*** hypotension, particularly at MAP <65 mm Hg or >20% less than baseline; Relative (to baseline) thresholds were not superior to absolute thresholds
Maheshwari and colleagues[12] (2018)	Retrospective cohort, single centre, *n*=42 825 patients	MAP <65 mm Hg before or after skin incision	Five percent increased risk of AKI for each doubling of the duration of hypotension; hypotension occurred more frequently before (i.e. ***preoperatively***), than after (i.e. ***intraoperatively***), skin incision
Tang and colleagues[30] (2019)	Retrospective cohort; single centre; *n*=4952 patients <60 yr of age	Intraoperative MAP <75, 70, 65, 60, or 55 mm Hg	Risk of AKI was associated with both severity and duration of ***intraoperative*** hypotension
Khanna and colleagues[31] (2019)	Retrospective cohort of 2833 postoperative patients in an ICU; single centre	Lowest daily MAP (continuous variable)	Risk of AKI was greater for patients with lower ***postoperative*** MAP
Liao and colleagues[32] (2020)	Retrospective cohort of patients who underwent liver resection; single centre; *n*=796 patients	Lowest absolute MAP <65 mm Hg for more than 10 cumulative minutes during surgery	Risk of AKI was independently associated with ***intraoperative*** hypotension
Loffel and colleagues[33] (2020)	Retrospective cohort of patients undergoing major urological surgery; single centre; *n*=416	Duration of MAP <65, 60, or 55 mm Hg after induction of anaesthesia	Risk of AKI was associated with both severity and duration of hypotension; substantial periods of hypotension occurred both before (***preoperative***) and after (***intraoperative***) skin incision
Park and colleagues[34] (2020)	Three retrospective cohorts of patients undergoing noncardiac surgery; multiple centre; *n*=45 520, 29 704, and 7435	Lowest intraoperative MAP	Risk of AKI was associated with lowest MAP in patients whose intraoperative MAP fell below 65 mm Hg, but not in those whose MAP remained ≥65 mm Hg; variability of MAP was also associated with AKI
Gregory and colleagues[19] (2021)	Retrospective cohort; multicentre; *n*=368 222 surgical procedures	Intraoperative MAP <75, 65, or 55 mm Hg, or >20% or 40% below baseline	Risk of AKI was associated with severity of ***intraoperative*** hypotension, detectable even at the 75 mm Hg threshold

Continued

Table 1 Continued

Authors	Setting	Definition of hypotension/intervention	Findings in relation to AKI
Khanna and colleagues[35] (2021)	Retrospective cohort; multicentre; *n*=67 968 surgical procedures	Postoperative MAP <75, 65, or 55 mm Hg	Risk of Stage II/II AKI was associated with severity of ***postoperative*** hypotension, detectable even at the 75 mm Hg threshold and even in patients who did not experience intraoperative hypotension (i.e. MAP ≤65 mm Hg)
Kluger and colleagues[36] (2022)	Retrospective cohort; single centre; *n*=1063 patients undergoing emergency hip surgery	Duration of intraoperative MAP ≤75, 70, 65, 60, or 55 mm Hg	No significant association was found between ***intraoperative*** hypotension and AKI, but in this cohort intraoperative hypotension was uncommon
Systematic reviews and meta-analyses:		Definition of hypotension	
Gu and colleagues[37] (2018)	Meta-analysis of 14 cohort studies, with two reporting AKI as an outcome (*n*=38 457 patients)	Various definitions based on severity and duration	***Intraoperative*** hypotension was associated with 39% increased risk of AKI
Wesselink and colleagues[38] (2018)	Systematic review of 42 relevant publications, with 12 reporting AKI as an outcome	Various definitions based on severity and duration	Increased risk of AKI when ***intraoperative*** MAP was < 65 mm Hg, with risk positively associated with both severity and duration of hypotension
Wijnberge and colleagues[39] (2021)	Systematic review and meta-analysis of 7273 patients across eight studies	Various definitions based on severity and duration	***Intraoperative*** hypotension was associated with a 2.69-fold excess risk of AKI
RCTs		Intervention	
Schmid and colleagues[40] (2016)	Major abdominal surgery (*n*=180); single centre	Algorithm-guided goal-directed haemodynamic therapy	Goal-directed therapy was not superior to standard care with regard to postoperative renal function or to rate of achievement of ***intraoperative*** and ***postoperative*** haemodynamic goals
Futier and colleagues[41] (2017)	High-risk patients (*n*=292); multicentre	Individualised management strategy	An individualised management strategy to avoid ***intraoperative*** hypotension reduced the risk of postoperative organ dysfunction, including AKI
Wu and colleagues[42] (2017)	Hypertensive patients 65–80 yr undergoing major gastrointestinal surgery (*n*=646); multicentre	Target MAP of 65–79, 80–95, or 96–110 mm Hg achieved using vasoactive agents	An ***intraoperative*** target MAP of 80–95 mm Hg was associated with lesser risk of AKI than lower or higher target MAP
Davies and colleagues[43] (2019)	Urgent hip surgery (*n*=240)	Stroke volume optimisation and maintenance of MAP within 30% of its baseline value	The ***intraoperative*** intervention was not significantly associated with reduced incidence of postoperative organ dysfunction, including AKI, or with significantly lesser area under the curve for MAP below 30% of baseline
Schmid and colleagues[44] (2019)	Patients ≥60 yr undergoing hip surgery (*n*=127); single centre	A multisystem optimisation protocol that included maintenance of MAP >70 mm Hg	The intervention, delivered across the ***preoperative***, ***intraoperative***, and ***postoperative*** periods, was associated with a 63% reduction in risk of AKI
Tu and colleagues[45] (2021)	Meta-analysis of the five RCTs described previously (*n*=1485)	Strict BP management (MAP > 70 mmHg)	Strict BP management was associated with a 27% reduction in the risk of AKI
Guo and colleagues[46] (2020)	Patients ≥65 yr undergoing gastrointestinal tumour resection (*n*=162); single centre	Continuous infusion of methoxamine (2 μg kg^{-1} min^{-1}) from before induction of anaesthesia	Methoxamine infusion was associated with greater ***intraoperative*** MAP and reduced incidence of AKI
Cardiac surgery requiring CPB			

Continued

Table 1 Continued

Authors	Setting	Definition of hypotension/intervention	Findings in relation to AKI
Primary publications (observational)		Definition of hypotension	
Abel and colleagues[47] (1976)	Retrospective cohort of 500 consecutive patients who survived beyond 24 h of surgery; single centre	Lowest MAP measured during CPB (as a continuous variable)	Lowest arterial pressure ***during CPB*** was not associated with postoperative renal dysfunction; however, MAP ***in the operating theatre immediately before transfer to the ICU*** was associated with postoperative renal dysfunction
Slogoff and colleagues[48] (1990)	Retrospective cohort of 511 patients undergoing mildly hypothermic CPB (28–32°C); single centre	Area under the curve for MAP <50 mm Hg (as a continuous variable)	Hypotension ***after CPB***, but not hypotension ***during CPB***, was associated with postoperative renal dysfunction
Fischer and colleagues[49] (2002)	Retrospective cohorts of patients undergoing mildly hypothermic CPB (32–34°C) who had normal postoperative renal function (n=48) or postoperative renal dysfunction either not requiring (n=51) or requiring (n=44) haemofiltration/dialysis; single centre	Duration of MAP <60 mm Hg during CPB (continuous variable)	Patients who developed postoperative acute renal failure or renal dysfunction experienced longer periods ***during CPB*** at MAP <60 mm Hg
Lombardi and Ferreiro[50] (2008)	Prospective cohort of 4118 patients undergoing cardiac surgery; single centre	MAP during CPB (continuous variable)	AKI was independently associated with the lowest MAP ***during CPB*** in patients without, but not with, preoperative renal dysfunction (creatinine clearance <60 ml min^{-1} [1.73 $m]^{-2}$)
Kanji and colleagues[51] (2010)	Prospective cohort of 157 consecutive high-risk patients undergoing CABG or valve surgery with permissive hypothermic (>33°C) CPB; single centre	Difference between preoperative MAP and average MAP during CPB (continuous variable)	AKI was independently associated with the difference between MAP ***during CPB*** and baseline MAP
Haase and colleagues[52] (2012)	Retrospective cohort of 920 patients undergoing cardiac or aortic surgery requiring CPB; single centre	>75th percentile for the area under the curve for MAP <50 mm Hg during CPB	Hypotension ***during CPB*** was not significantly associated with postoperative AKI, although there was a trend for this in patients with severe anaemia
Sirvinskas and colleagues[53] (2012)	Prospective cohort of 122 randomly selected older (≥70 yr) patients undergoing CABG surgery with mild hypothermic (≥34°C) CPB	MAP during CPB (continuous variable)	Postoperative renal function did not differ significantly between patients whose MAP ***during CPB*** was maintained at <60 (n=36), 60–70 (n=36), or >70 mm Hg (n=50)
Aronson and colleagues[54] (2013)	Retrospective cohort of 7247 patients who underwent CABG surgery with mildly hypothermic (30–32°C) CPB; single centre	Systolic pressure relative to baseline (continuous variable)	The postoperative increase in serum creatinine varied with the magnitude of relative hypotension ***during the periods before and after CPB***
Ono and colleagues[55] (2013)	Prospective cohort of 480 patients undergoing CABG surgery; single centre	Arterial pressure below the lower limit of cerebral autoregulation, as determined by near-infrared spectroscopy	MAP below the lower limit of cerebral autoregulation, but not absolute MAP, ***during CPB***, was independently associated with AKI, that is, patients who developed AKI had higher lower limits of cerebral autoregulation during CPB
Sickeler and colleagues[56] (2014)	Retrospective cohort of 3963 patients undergoing CABG or valve surgery with mild hypothermic CPB (target 32°C); single centre	>75th percentile for the area under the curve for MAP <50 mm Hg during CPB	No excess risk of AKI was detected for patients who experienced hypotension ***during CPB***, regardless of the presence or absence of anaemia
Rettig and colleagues[57] (2017)	Retrospective cohort of 1891 patients undergoing CABG surgery with mild hypothermic CPB (32–35°C); single centre	Various definitions based on severity and duration	Duration of MAP ≤50 mm Hg or ≤60% of baseline ***during CPB*** was associated with AKI in univariable, but not multivariable, analysis
	Retrospective cohort of 513 patients who underwent CPB; single centre	Duration over which mean perfusion pressure (MAP−central venous pressure) was >20%	AKI was independently associated with the duration of hypotension ***during CPB***

Continued

Table 1 Continued

Authors	Setting	Definition of hypotension/intervention	Findings in relation to AKI
Hu and colleagues[58] (2020)		less than that before anaesthesia (continuous variable)	
RCTs		Intervention	
Urzua and colleagues[59] (1992)	Patients undergoing elective CABG with CPB (n=21)	Phenylephrine infusion to maintain MAP >70 mm Hg ***during CPB***	The rate of AKI did not differ between the groups
Azau and colleagues[60] (2014)	Patients undergoing elective cardiac surgery with CPB (n=300)	High (75–85 mm Hg) *vs* low (50–60 mm Hg) MAP ***during CPB***	The rate of AKI did not differ between the groups

complication of cardiac surgery, with the global incidence estimated at 22.3%, with 2.3% requiring dialysis.[5] Hypotension in the perioperative period is potentially a major factor in the pathophysiology of postoperative AKI.[6]

Here, we review current knowledge of the incidence of perioperative hypotension and its possible impact on kidney perfusion and function. Our initial literature search using Ovid MEDLINE, with keywords (hypotension) AND (acute kidney injury OR renal circulation), retrieved 1680 articles available on December 14, 2021 (no lower date limit). These articles, and others identified by the authors, were included based on the narrative of the review. The PeriOperative Quality Initiative has recently generated consensus statements regarding management of arterial pressure during the preoperative,[7] intraoperative,[8] and postoperative[9] periods. We refer the reader to these articles and relevant jurisdictional guidelines for specific recommendations regarding management of patients. Rather, the focus of this article is to identify current critical knowledge gaps and proposed future directions for clinical and basic research, having first briefly reviewed established knowledge. When relevant, we consider cardiac and noncardiac surgical procedures separately, as important differences in both aetiology and management of perioperative hypotension exist between these surgical modalities, chiefly because of the typical use of cardiopulmonary bypass (CPB) during cardiac procedures.

Established knowledge

Perioperative hypotension is common

Preoperative hypotension

Hypotension, depending on definition, occurs in 9–53% of patients during the 'preoperative period' from induction of anaesthesia to before the first surgical incision.[10–13] Risk of preoperative hypotension appears to be exacerbated when pre-induction MAP is low (<70 mm Hg), when propofol is deployed for induction, when larger doses of fentanyl are used in older patients,[10,11,13] and when surgery is deemed emergency.[11] Preoperative hypotension can also be promoted by head-up tilt, reduced cardiac filling caused by mechanical ventilation, preoperative hypovolaemia, and anaphylactic responses to medications.[14] Hypotension is also encountered in around 30% of patients as a side-effect of spinal anaesthesia.[15]

Intraoperative hypotension

During surgery, hypotension can be caused by anaesthesia or by hypovolaemia attributable to blood loss, cardiac dysfunction, systemic vasodilatation, and aspects of the surgical intervention itself.[16] It can also be secondary to vasoplegia, a problem particularly associated with CPB, with an incidence of 5–25%.[17,18]

In a recent large (368 222 procedures) retrospective multicentre analysis of noncardiac surgery, MAP ≤75 mm Hg occurred in 39.5% of cases, ≤65 mm Hg occurred in 19.3% of cases, and ≤55 mm Hg occurred in 7.5% of cases.[19] An even greater incidence (61.0% <65 mm Hg) was found in a recent large multicentre analysis of intraoperative arterial pressure (4750 patients ≥65 yr of age).[20]

Postoperative hypotension

During the hours and days postoperatively, hypotension can be secondary to hypovolaemia, cardiac dysfunction, and

vasoplegia. Postoperative vasoplegia is particularly common after cardiac surgery[17] and in patients who develop sepsis.[21]

If arbitrarily defined as a systolic BP <90 mm Hg within 24 h after surgery, hypotension has been reported in >30% of patients.[22,23] Using the same definition, hypotension during postoperative days 1–4 occurred in around 8% of patients.[22,23] However, because arterial pressure is often only monitored periodically in the postoperative ward, the incidence of postoperative hypotension is commonly underestimated.[24] For example, routine monitoring (4-hourly) of MAP after abdominal surgery detected hypotension (<65 mm Hg) in only about 50% of the patients who actually experienced MAP <65 mm Hg for at least 15 min.[24] Thus, there is a strong rationale for increasing the intensity of measurement of MAP in the postoperative period, although the feasibility of this approach is limited by availability of resources[9] and by uncertainty regarding the optimal monitoring modality (e.g. invasive monitoring or wearable sensors).[25]

Perioperative hypotension is associated with postoperative acute kidney injury

In noncardiac surgery, there is strong evidence for associations between AKI and the severity and duration of hypotension in the preoperative, intraoperative, and postoperative periods (Table 1).[26–60] Furthermore, some interventions to avoid perioperative hypotension have been found to reduce the incidence of AKI (Table 1). In cardiac surgery, there is evidence of association between patient-specific definitions of intraoperative hypotension, both during CPB and during the periods before and after CPB, and AKI (Table 1). However, there is little evidence of an association with absolute levels of MAP during CPB. Two small-scale clinical trials have not demonstrated reduced incidence of AKI with interventions to increase MAP during CPB.[59,60]

The kidney is susceptible to ischaemia and hypoxia during hypotension

The pathophysiology of AKI is complex. Nevertheless, there is strong evidence that ischaemia and hypoxia are major factors in multiple aetiological forms of AKI.[61] Thus, greater understanding of the mechanisms linking hypotension and renal ischaemia and hypoxia has the potential to guide interventions to avoid or attenuate AKI. Under resting physiological conditions, renal blood flow (RBF) accounts for 20–25% of cardiac output, and renal fractional extraction of oxygen is remarkably low (10–20%).[62] Thus, relative to other major organs, the kidneys are well perfused relative to metabolic requirements.[62] Nevertheless, at least 12 factors that are consequences of renal structure, renal function, or perioperative conditions act in concert to render the kidneys, particularly the renal medulla, susceptible to ischaemia and hypoxia during perioperative hypotension.

Structural factors

Oxygen delivery to tissue appears to be limited by the density of peritubular capillaries, and thus the surface area available for oxygen transport from the vasculature to the parenchyma.[63]

Blood flow per unit of tissue weight is relatively low in the renal medulla, being around 10% of cortical blood flow in the outer medulla and around 1% in the inner medulla.[64]

Diffusive oxygen shunting from afferent to efferent vessels in the renal cortex (arteries to veins) and medulla (descending-to-ascending vasa recta) reduces oxygen delivery to tissue.[65]

In the outer medulla, the tubular elements chiefly responsible for active sodium reabsorption, the thick ascending limbs of the loop of Henle, are situated at the periphery of the vascular bundles (Fig 1). Furthermore, the relatively oxygen-rich descending vasa recta are mainly sequestered into the core of the vascular bundles, so are the furthest vascular elements from the thick ascending limbs.[68]

Functional factors

Active sodium reabsorption accounts for around 80% of renal oxygen consumption (RVO_2) under resting physiological conditions.[69] Thus, efforts to increase glomerular filtration rate (GFR) in patients with AKI could exacerbate renal hypoxia.[70]

The kidneys have limited ability to mount a hyperaemic response to tissue hypoxia.[70]

The adult kidney has poor capacity for angiogenesis, and thus vascular repair after injury.[71]

Renal ischaemia can cause aggregation of erythrocytes within medullary vasa recta, especially in the capillary plexus of the inner stripe, leading to vascular congestion.[72] Consequently, medullary ischaemia continues even after blood flow to the kidneys is restored ('no reflow').[72]

The major mechanism protecting the kidneys from ischaemia and hypoxia during hypotension is autoregulation of RBF.[73] RBF is relatively well autoregulated, notably within the 80–180 mm Hg range.[74] However, the lower limit of whole-kidney autoregulation appears to be higher than that of cerebral autoregulation.[75]

Renal medullary blood flow is poorly autoregulated.[64]

Factors specific to the perioperative period

Anaesthesia reduces RBF in experimental animals[76] and humans,[77] thus reducing renal oxygen delivery (RDO_2). In anaesthetised animals, renal tissue oxygenation cannot be maintained unless systemic oxygen delivery is supplemented by hyperoxic ventilation,[78] as is standard clinical practice. RBF and thus RDO_2 are further reduced during CPB,[79] leading to renal medullary hypoxia.[80,81]

Renal autoregulation is blunted by multiple preoperative and intraoperative factors. It is impaired in chronic hypertension,[74] chronic kidney disease,[74] diabetes,[74] atherosclerotic renal artery stenosis,[82] and ageing.[83] It is also impaired during AKI induced by ischaemia–reperfusion injury,[84] although apparently not altered during ovine sepsis.[85] In addition to decreasing RBF *per se*, some (but not all) anaesthetics blunt autoregulation of RBF.[86,87] Furthermore, intraoperative factors, such as haemodilution,[88] hypothermia,[89] and renal tissue hypoxia,[90] can blunt renal autoregulation. Vasopressor agents can also alter renal autoregulation.[85] Thus, multiple factors likely hinder maintenance of RBF during perioperative hypotension.

Knowledge gaps

There is no standard definition of perioperative hypotension

This knowledge gap exists with regard to the preoperative,[7] intraoperative,[8] and postoperative periods,[9] although most

published research relates to the intraoperative period. It is a consequence both of the variable definitions used across published studies and the absence of an identifiable level of MAP at which risk of organ damage is minimised.

A recent consensus statement identified an intraoperative MAP target of >60–70 mm Hg rather than ≤60 mm Hg as being associated with better outcomes for adults undergoing noncardiac surgery, including lesser incidence of AKI.[8] However, it was not possible to recommend a specific level of MAP at which therapy should be initiated. Indeed, a systematic review identified 140 different definitions of intraoperative hypotension.[91] Based on the varied definitions used, the incidence of intraoperative hypotension varied widely, from 5% to 99%. Thus, there is a clear need for standardisation of definitions, although the available evidence base for establishing such definitions is inadequate.[23,29,92] This uncertainty regarding management of intraoperative hypotension may have important implications for patient outcomes, as the associated risk of postoperative complications, including AKI, also varies with the definition of intraoperative hypotension.[93]

There have been attempts to identify specific lower limits of intraoperative[26,27,29] and postoperative[19,31,35] MAP to avoid

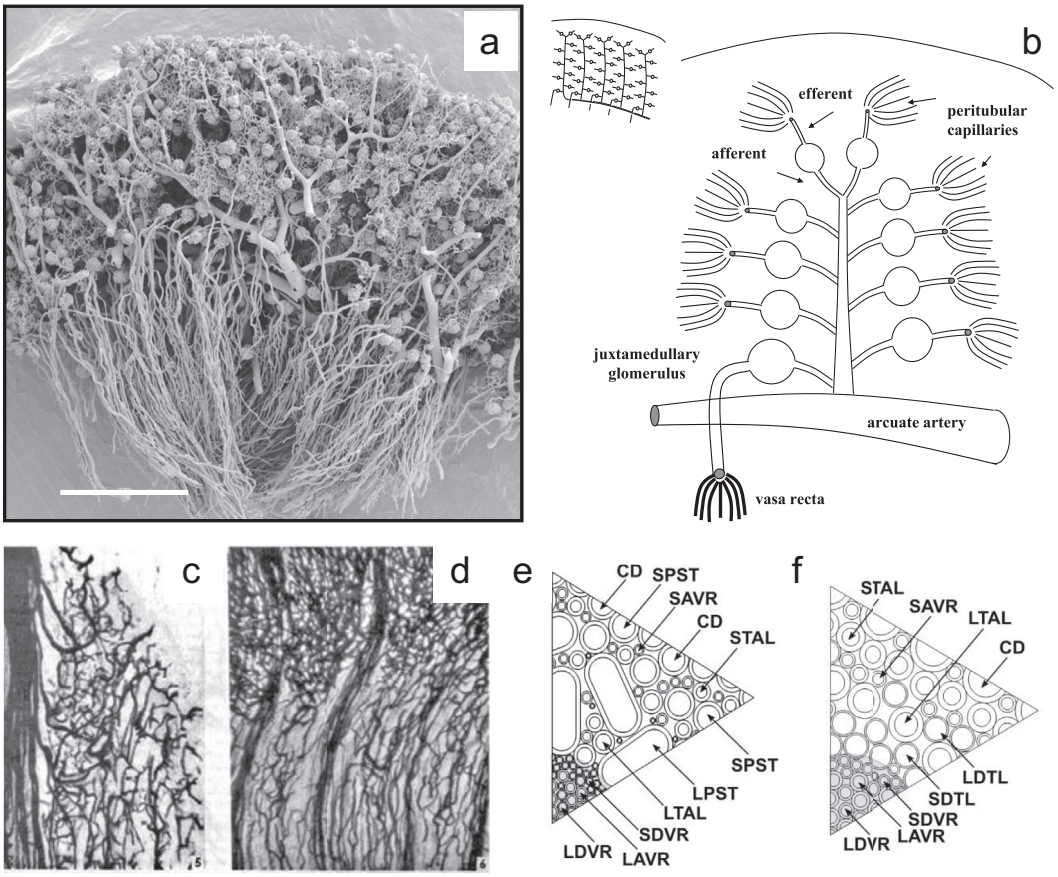

Fig 1. Renal circulation. (a) Scanning electron microscope image of a resin cast of a portion of the renal circulation of the rabbit showing the cortex and medulla (scale bar=1 mm). Note the vascular bundles (of vasa recta) arising from the efferent arterioles of juxtamedullary glomeruli. (b) A schematic diagram of the architecture of the renal cortex. Note that afferent arterioles arise from the interlobular arteries. The vasa recta arise from the efferent arterioles of glomeruli at the border of the cortex and medulla (juxtamedullary glomeruli, around 10% of the total population of glomeruli). Thus, blood flow to the renal medulla can be regulated independently from blood flow to the majority of the renal cortex. (c) and (d) Axial views of the vascular bundles of the outer renal medulla of the rat. Note the plexus of capillaries in the inner stripe shown in detail in (c), composed of short vasa recta, with long vasa recta sequestered to the centre of the vascular bundles shown in (d). Thus, blood flow may be independently regulated within the inner and outer medulla. (e) and (f) Schematic diagram of the topography (radial view) of vascular and tubular elements in the (e) outer and (f) inner stripe of the outer medulla, showing the sequestration of long ascending and descending vasa recta within the centre of the vascular bundle and the position of tubular elements (thick ascending limbs of the loop of Henle and collecting ducts) at the periphery of the vascular bundles, so at some distance from their source of oxygen. CD, collecting duct; LAVR, long ascending vasa recta; LDTL, long descending thin limbs of the loop of Henle; LDVR, long descending vasa recta; LPST, long proximal straight tubules; LTAL, long thick ascending limbs of the loop of Henle; SAVR, short ascending vasa recta; SDTL, short descending thin limbs of the loop of Henle; SDVR, short descending vasa recta; SPST, short proximal straight tubules; STAL, short thick ascending limbs of the loop of Henle. Images reproduced with permission from (a and b) Evans and colleagues,[66] (c and d) Pallone and colleagues,[64] and (e and f) Lee and colleagues.[67]

Table 2 Inotropes, inodilators, and vasopressor agents used for treatment of perioperative hypotension. Unless otherwise stated, all opinions were compiled from previous works.[14,17,99] Second-line vasopressors are used when patients are found to be refractory to a first-line vasopressor.

A. Inotropes and inodilators		**Indication: Hypotension associated with low cardiac output**	
Agent	**Pharmacology**	**Advantages**	**Disadvantages and contraindications**
Epinephrine	Directly acting β- and α-adrenoceptor agonist (endogenous)	Increases arterial pressure by both increasing cardiac output and vascular resistance	Can induce supraventricular and ventricular arrhythmias, hyperglycaemia, hyperlactataemia, and severe hypertension; Relatively contraindicated in patients on β-blocker therapy or with cardiac ischaemia
Norepinephrine	Combined β- and α-adrenoceptor agonist with greater α effect (endogenous)	Increases arterial BP by vasoconstriction and maintained or slightly increased cardiac output	Can contribute to arrhythmias
Metaraminol	Effect on α-adrenoceptors and induction of endogenous norepinephrine release	Often given peripherally with little risk of tissue necrosis if extravasated; often used as bolus therapy	Can induce tachyphylaxis and thus lose efficacy
Dopexamine	Stimulates β_2-adrenoceptors and peripheral dopamine D_1- and D_2-receptors	Chronotropic and inotropic action; also inhibits norepinephrine reuptake	Increases risk of tachycardia and nausea
Vasopressin	Stimulates vasopressin (V_1 and V_2) receptors	Increases vasoconstriction (especially the splanchnic territory) and water reabsorption	Increases BP; increases urinary concentration
Isoprenaline (isoproterenol)	Direct and non-selective β-adrenoceptor agonist	Positive inotropic and chronotropic effects and reduced diastolic pressure by lowering total peripheral resistance	Can induce arrhythmias and hypotension; relatively contraindicated in patients on β-blocker therapy or with cardiac ischaemia
Dobutamine	β_1-selective agonist	Has similar inotropic but weaker chronotropic actions than epinephrine	Vasodilatation at lower doses compensated by increased cardiac output; relatively contraindicated in patients on β-blocker therapy or with cardiac ischaemia
Ephedrine	Indirect α- and β-adrenoceptor agonist	Longer duration of action than epinephrine; increases cardiac output and total peripheral resistance	Potential for tachyphylaxis attributable to depletion of neuronal stores of norepinephrine; typically administered as boluses; relatively contraindicated in patients on β-blocker therapy or with cardiac ischaemia
Dopamine	Broad-spectrum dopamine receptor agonist with some α- and β-adrenoceptor agonist activity (endogenous)	Low-dose dopamine can induce renal and splanchnic vasodilatation	Can have β_1- and α_1-adrenoceptor agonist activity according to dose (mostly α_1 at higher doses); contraindicated in patients

Continued

Table 2 Continued

A. Inotropes and inodilators		Indication: Hypotension associated with low cardiac output	
Agent	**Pharmacology**	**Advantages**	**Disadvantages and contraindications**
			with pheochromocytoma, uncorrected tachyarrhythmia, or ventricular fibrillation
Levosimendan	Increases the sensitivity of cardiac contractile proteins to calcium and opens ATP-dependent potassium channels; acts as an inodilator	Increases cardiac output; may increase glomerular filtration rate more than dobutamine[100]	Can induce hypotension with loading; typically used in the context of cardiac surgery; may improve BP in patients with cardiac failure by increasing cardiac output
Milrinone	Inhibits phosphodiesterase in cardiac and vascular muscle; acts as an inodilator	Increases cardiac output	Typically used in the context of cardiac surgery; may improve BP in patients with cardiac failure by increasing cardiac output
B. Vasopressors		**Indication: Hypotension associated with adequate cardiac output**	
Agent	**Pharmacology**	**Advantages**	**Disadvantages and contraindications**
Norepinephrine	Combined β- and α-adrenoceptor agonist with greater α effect (endogenous)	First-line vasopressor; minimal chronotropic effects and net impact on cardiac output	Can induce peripheral ischaemia and severe hypertension
Phenylephrine	Directly acting and highly selective α-adrenoceptor agonist	First-line vasopressor; no direct effects on HR or cardiac contractility	Can induce reflex bradycardia
Metaraminol	Direct α-adrenoceptor agonist, which also stimulates release of norepinephrine from sympathetic nerves	First-line vasopressor; no direct effects on HR or cardiac contractility	Can induce reflex bradycardia
Methoxamine	Direct α-adrenoceptor agonist	First-line vasopressor; relatively long duration of action	Can induce reflex bradycardia
Vasopressin	V_2- and V_1-receptor agonist (endogenous)	Second-line vasopressor; causes less direct coronary and cerebral vasoconstriction than norepinephrine; in contrast to α-adrenoceptor agonists, it also appears to maintain potency under acidotic conditions	Can decrease cardiac output and induce excessive peripheral vasoconstriction; V_2-mediated effects have the potential to cause water retention
Terlipressin	Long-acting V_1-receptor agonist	Second-line vasopressor; in addition to those for vasopressin, it is long acting and does not cause V_2-mediated water retention	Can decrease cardiac output and induce excessive peripheral vasoconstriction
Angiotensin II	AT_1- and AT_2-receptor agonist (endogenous)	Second-line vasopressor; has the potential to support glomerular filtration rate through selectively increased post-glomerular vascular resistance	Potential for renal vasoconstriction; contraindicated for patients on angiotensin receptor blocker therapy

postoperative complications. However, these have mainly been observational studies, so interpretation is confounded by the inability to dissociate the risk associated with hypotension from the risk associated with the interventions used to restore MAP. It also appears likely that the deleterious effects of specific levels and durations of hypotension vary according to the characteristics of the patient, the nature of the surgical procedure, and the epoch of the surgical procedure in which it occurs. Furthermore, with regard to prediction of AKI, thresholds of MAP based on change from preoperative MAP are not necessarily superior to those based on absolute levels of MAP.[29] Similarly, with regard to MAP during CPB, there is uncertainty regarding optimal targets.[94] Thus, there is a need to more thoroughly identify optimal levels of MAP during the preoperative, intraoperative, and postoperative periods. Given that the major dangers imposed by hypotension in a surgical setting are ischaemia and hypoxia,[95] a working definition based on the lower limit of autoregulation of vital organs seems reasonable.[73] Brady and colleagues[96] suggested a method based on monitoring autoregulation of cerebral blood flow using near-infrared spectroscopy (NIRS). But, autoregulatory capacity varies between individuals and organs, and with the range of (patho-) physiological states encountered during the perioperative period. For the kidneys, it also appears to vary between intra-organ vascular territories, being poorer in the medulla than the cortex. Thus, although monitoring cerebral autoregulation may provide insights into protection from AKI,[55] it is not the same as monitoring renal circulatory function, for which we have few available clinical tools (see in next paragraph).

When should we intervene to protect the kidney?

The central question here is, 'What is the lower limit of renal autoregulation in the perioperative period?' Unfortunately, this simple question does not have a straightforward answer. It is complicated by the fact that renal autoregulation is mediated by multiple mechanisms operating over different timescales.[74] It is further complicated by the dearth of information from humans, and thus reliance on observations in experimental animals. We must also consider the multiple vascular territories within the kidney and their potential for differential autoregulation (Fig 1).[64] The lower limit of autoregulation of RBF varies between species and probably also experimental conditions, but, at least in some species, it appears to be only slightly less than conscious, resting MAP.[97,98] If this is also true of humans, any MAP less than its preoperative level would put the kidney, and particularly the medulla, at risk of ischaemia and hypoxia. A rational regimen for intervention should also include consideration of comorbidities, such as preoperative renal insufficiency, diabetes, hypertension, and heart failure, as these likely exacerbate the susceptibility of the kidney to hypotension-induced injury.

How should we intervene?

Perioperative therapy to support MAP appears to reduce risk of postoperative complications, including AKI.[41] However, there is limited information to guide choice of specific therapies (Table 2).[99,100] MAP can be elevated by increasing cardiac output or total peripheral resistance. However, although vasopressors can increase perfusion pressure, they can also impede perfusion. A further complication is the presence of three distinct renal vascular territories, partly in series and partly in parallel: the cortex, outer medulla, and inner medulla (Fig 1). Given the susceptibility of the medulla to hypoxic injury,[61] an ideal 'kidney-protective' therapy would preserve the medullary circulation. Unfortunately, the effects of available therapies for hypotension on renal perfusion and oxygenation have been little studied.[17] However, two lines of research provide relevant information (Table 3),[101–119] albeit without robust evidence to support specific interventions. The first is clinical observations of patients equipped with a renal venous catheter to allow measurement of RBF, RDO_2, and RVO_2. The second is from experimental studies in animals additionally equipped for real-time measurement of intrarenal perfusion and oxygenation. Although such observations in experimental animals may not be directly applicable to the clinical situation, they provide mechanistic insights not currently available from clinical studies.

Fluids

Crystalloids and colloids increase extracellular fluid, plasma volume, or both, and thus venous return and stroke volume, so are useful in patients who are hypovolaemic. However, because they can increase venous pressure, they can also hinder organ perfusion. In patients after cardiac surgery, fluid loading with either a crystalloid or colloid modestly increased MAP (by 5–10 mm Hg)[101,120,121] and RBF, but did not improve RDO_2, in part because of the associated haemodilution, which was particularly marked with the colloid.[101] The crystalloid also increased GFR. Consequently, fractional renal oxygen extraction increased, indicating a relative deficit in RDO_2.[101] Similar observations with crystalloids have been reported in both healthy sheep[102] and sheep with sepsis.[103] However, in these experimental studies, fluid therapy was found to increase renal medullary tissue P_{O_2}. Thus, although crystalloid therapy does not appear to improve whole-kidney oxygenation, it may benefit the renal medulla.

Inotropes and inodilators

Inotropes, such as epinephrine and dobutamine, act chiefly via agonism of beta-adrenoceptors to increase cardiac contractility (β_2) and HR (β_1).[99] Some of these agents also enhance ventricular relaxation during diastole (lusitropy). So-called inodilators, which include dopamine and levosimendan, also induce vasodilation. Inotropes or inodilators are often used to increase cardiac output and MAP after cardiac surgery, and are sometimes given prophylactically, in patients with low cardiac output syndrome, as part of goal-directed therapy.[122] They are also used for support of weaning from CPB.[123] Choice of agent and dose in this setting is mainly driven by concerns about the potential for myocardial hypoxia attributable to increased myocardial oxygen consumption.[122,123] Other potential adverse effects include tachycardia and atrial fibrillation, and in the case of inodilators, the potential for exacerbation of hypotension.[122,123] They have been remarkably little studied in the context of renal haemodynamics and function.

Dopamine increased RBF and thus RDO_2, without affecting GFR and thus RVO_2, in patients after cardiac surgery.[105] Thus, it reduced the renal fractional extraction of oxygen, thus promoting renal oxygenation at the whole-kidney level. However, it failed to increase RBF in porcine experimental CPB.[106] Low-dose dopamine also caused renal vasoconstriction in patients with AKI.[124] Increased medullary blood flow during dopamine therapy appears to be counterbalanced by

Table 3 Effects of standard and potential therapies for perioperative hypotension on renal oxygenation and its determinants. Inclusion criteria: at least a measure of renal blood flow. ↓, reduced; ↑, increased; ↔, no significant change. Empty cells are attributable to unavailability of data for that specific variable. AKI, acute kidney injury; CPB, cardiopulmonary bypass; FEO_2, renal fractional oxygen extraction; GFR, glomerular filtration rate; Po_2, oxygen tension; RBF, renal blood flow; RDO_2, renal oxygen delivery; RVO_2, renal oxygen consumption.

Agent	Species	Condition	References	RBF	GFR	RDO_2	RVO_2	FEO_2	Cortical Po_2	Medullary Po_2	Urinary Po_2
Fluids											
Crystalloid	Human	After cardiac surgery	Skytte Larsson and colleagues[101]	↑	↑	↔	↑	↑			
Crystalloid	Sheep	Healthy	Lankadeva and colleagues[102]	↔	↑	↔	↑	↑	↔	↑	↑
Crystalloid	Sheep	Sepsis	Lankadeva and colleagues[103]	↔	↑	↔	↔	↔	↔	↑	↑
Colloid	Human	After cardiac surgery	Skytte Larsson and colleagues[101]	↑	↔	↔	↔	↔			
Inotropes and inodilators											
Epinephrine	Sheep	Sepsis	Di Giantomasso and colleagues[104]	↓	↔						
Dopamine	Human	After cardiac surgery	Redfors and colleagues[105]	↑	↔		↔	↓			
Dopamine	Pig	During CPB	Mackay and colleagues[106]	↔							
Dopamine	Rat	Euvolaemic	Heyman and colleagues[107]	↔						↔	
Levosimendan	Human	After cardiac surgery	Bragadottir and colleagues[108]	↑	↑		↔	↔			
Levosimendan	Human	AKI after cardiac surgery	Tholen and colleagues[109]	↑	↔						
Vasopressor agents											
Norepinephrine	Human	Vasodilatory shock after cardiac surgery	Redfors and colleagues[110]	↔	↑	↑	↔	↓			
Norepinephrine	Human	After liver transplantation	Skytte Larsson and colleagues[111]	↑	↑	↑	↑	↔			
Norepinephrine	Sheep	Healthy	Calzavacca and colleagues[112]	↔		↔	↑	↔	↓	↓	
Norepinephrine	Sheep	Sepsis	Lankadeva and colleagues[113]	↔	↔	↔	↔	↔	↔	↓	↓
Phenylephrine	Sheep	Healthy	Morimatsu and colleagues[114]	↑							
Phenylephrine	Sheep	Sepsis	Morimatsu and colleagues[114]	↑							
Metaraminol	Sheep	During CPB	Lankadeva and colleagues[80]	↑	↑	↑	↑	↔	↑	↑	
Vasopressin	Human	After cardiac surgery	Bragadottir and colleagues[115]	↓	↑		↑	↑			
Vasopressin	Sheep	Healthy	Calzavacca and colleagues[112]	↓		↓	↔	↑	↔	↔	
Vasopressin	Sheep	Sepsis	Okazaki and colleagues[116]	↔	↔	↔	↔	↔	↔	↔	
Angiotensin II	Sheep	Healthy	Calzavacca and colleagues[112]	↓		↓	↔	↔	↔	↓	
Angiotensin II	Sheep	Sepsis	Lankadeva and colleagues[117]	↓	↑	↔	↔	↔	↔	↔	↔
N^G-methyl-L-arginine	Sheep	Sepsis	Ishikawa and colleagues[118]	↓	↓						
N^G-methyl-L-arginine	Rabbit	Anaesthetised	Sgouralis and colleagues[119]	↓					↓	↓	↓

increased solute load, and thus medullary oxygen consumption, so medullary tissue P_{O_2} is not increased.[107] Clinical trials using dopamine[125] or the D_1-receptors agonist fenoldopam[126] have failed to demonstrate improved renal outcomes.

Levosimendan, an inodilator, acts by increasing myocardial calcium sensitivity and opening ATP-dependent potassium channels in vascular smooth muscle.[127] In patients after cardiac surgery, levosimendan increased stroke volume and cardiac output but not MAP. It also increased RBF and GFR without significantly altering fractional renal oxygen extraction.[108] Thus, although levosimendan appears to improve renal perfusion and function by inducing renal vasodilation, it does not appear to improve the balance between oxygen supply and demand in the kidney. In patients with cardiac surgery-associated AKI, levosimendan increased RBF, but it also increased the requirement for norepinephrine.[109] Experimental studies of the effects of levosimendan on regional-kidney perfusion have not produced a clear consensus regarding its effects.[127] Nevertheless, levosimendan increased GFR under a range of clinical conditions, including decompensated heart failure, sepsis, and after cardiac surgery.[127] There is also evidence of pleiotropic effects, which may enhance renal perfusion and function.[128] Thus, although inodilators such as levosimendan and dopamine have no clinical role in the prevention of perioperative hypotension, they could potentially protect the kidney from the effects of hypotension. However, despite promising findings from small-scale clinical trials, the multicentre study of the Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients: A Multicenter Randomized Controlled Trial (CHEETAH) trial provided robust evidence of lack of benefit of levosimendan in patients undergoing on-pump cardiac surgery, including on the incidence of AKI.[129]

Vasopressor agents

Norepinephrine is the first-line vasopressor in many clinical situations. In addition to alpha-adrenoceptor-mediated vasoconstriction, it also has positive inotropic and chronotropic effects via beta-adrenoceptors.[110] In patients after cardiac surgery, infusion of norepinephrine to increase MAP from around 60 to around 75 mm Hg was accompanied by increased cardiac output, increased RDO_2, unchanged RVO_2 despite increased GFR, and reduced fractional renal oxygen extraction.[110] Similar effects were observed in patients after liver transplantation, although fractional renal oxygen extraction was unchanged.[111] In both cases, the improved renal function and oxygenation could be attributed to increasing MAP into the renal autoregulatory range.[110,111] Similar observations, regarding whole-kidney haemodynamics and oxygenation, were made during norepinephrine infusion in healthy sheep[112] and in sheep with sepsis.[113] However, in these experimental studies, norepinephrine induced renal medullary ischaemia and hypoxia. It also induced transient renal cortical vasoconstriction during experimental CPB in sheep.[130] Thus, although the renal effects of norepinephrine, when considered at the whole-kidney level, appear favourable, its effects on regional-kidney perfusion and oxygenation, and the attendant consequences for risk of AKI, merit further study.

Phenylephrine is a selective α_1-adrenoceptor agonist. Observations in humans indicate a tendency for reduced RBF but relatively well-maintained GFR, and thus increased filtration fraction.[131] In both healthy sheep and sheep with sepsis, pressor doses of phenylephrine had little impact on RBF,[114] having a similar profile of action on the kidney to that of norepinephrine under similar experimental conditions.[112,113] We are not aware of any relevant studies of the effects of phenylephrine on regional-kidney perfusion and oxygenation.

Metaraminol has both direct and indirect sympathomimetic effects. It is commonly used during CPB to achieve target MAP. In an ovine model of CPB, metaraminol dose-dependently increased systemic vascular resistance but not renal vascular resistance, resulting in increased RBF, RDO_2, and both medullary and cortical tissue P_{O_2}.[80] Thus, metaraminol may protect the kidney from ischaemia and hypoxia during CPB.

Arginine vasopressin (or its analogue terlipressin) is used chiefly as second-line vasopressor therapy in patients who are refractory to norepinephrine. However, its efficacy and safety as a first-line agent are becoming increasingly evident. In patients with vasoplegic syndrome after cardiac surgery (the Vasopressin Versus Norepinephrine for the Management of Shock After Cardiac Surgery [VaNCS] trial), use of vasopressin rather than norepinephrine reduced the incidence of mortality or severe postoperative complications, including AKI.[132] Vasopressin also tended to be superior to norepinephrine with regard to AKI in the Vasopressin and Septic Shock Trial (VASST) of patients with septic shock,[133] although no overall benefit in terms of mortality was detected.[134] However, vasopressin was not superior to norepinephrine in patients with cancer who developed septic shock, at least in terms of 28 day mortality or other major outcomes, including AKI, in the VaNCS II trial.[135] In a small clinical trial, vasopressin given prophylactically during and after CPB, in patients on angiotensin-converting enzyme inhibitor therapy, reduced the incidence of post-CPB hypotension and reduced norepinephrine requirements.[136] With regard to its renal effects, in patients after cardiac surgery, vasopressin dose-dependently increased GFR but decreased RBF, and thus impaired whole-kidney oxygen balance.[115] Vasopressin also reduces cardiac output,[116] which may be contraindicated in patients with hypotension.[115] Vasopressin decreased RBF and increased renal fractional oxygen extraction in both healthy sheep[112] and sheep with sepsis.[116] However, under both conditions, medullary tissue P_{O_2} was not reduced as it was by norepinephrine. Thus, despite apparent deterioration of global renal oxygenation during infusion of vasopressin, renal medullary oxygenation appears to be well preserved.

Angiotensin II is a potent vasopressor, which has been demonstrated to restore BP effectively and to improve renal function in experimental sepsis,[137] without exacerbating renal medullary hypoxia.[117] Angiotensin II is now emerging as an effective vasopressor to treat patients with catecholamine-resistant hypotension. In the Angiotensin II for the Treatment of High-Output Shock (ATHOS) trial, i.v. angiotensin II effectively increased BP and reduced catecholamine requirement in patients with vasodilatory shock.[138] There is also increasing interest in the use of angiotensin II in patients with vasoplegia after surgery.[139]

Collectively, the available literature regarding the renal effects of therapies for perioperative hypotension highlights the lack of a solid evidence base for when and which specific therapies should be used. Additional uncertainty arises from the fact that the effects of therapies on whole-kidney oxygenation do not necessarily reflect their effects on local renal tissue oxygenation. Thus, the lack of availability of methods to monitor intra-renal haemodynamics and oxygenation in the operating theatre, ICU, and general ward represents a major impediment to progress.

Future directions in detecting perioperative renal ischaemia and hypoxia

Available methods for measurement of RBF in patients have important limitations. The renal clearance of para-aminohippurate is confounded by its variable renal clearance. RBF can only be measured using haemodilution in patients equipped with a renal venous catheter/thermistor, requiring an invasive procedure. In an experimental setting, Doppler ultrasound-derived estimates of RBF showed little correlation with direct measurement of RBF with an implanted flow probe.[140] There are currently no validated methods for measurement of regional kidney perfusion or oxygenation in a surgical setting, although some indices derived from contrast-enhanced ultrasound may be useful.[141]

There has recently been interest in the use of NIRS for perioperative assessment of renal oxygenation. Its validity is supported by the relatively close agreement between renal oxygen saturation measured by NIRS and renal venous P_{O_2}.[142] The major limitation of this technique is that it can only be used in children and lean adults, as the 'skin-to-kidney distance' within which the NIRS signal actually reflects the state of the kidney is $\leq$4 cm. In addition, the renal NIRS signal mainly reflects cortical rather than medullary oxygenation.

Continuous measurement of urinary P_{O_2} has been proposed as a proxy measure of renal medullary tissue P_{O_2}.[143] Notably, urinary P_{O_2} correlates well with renal medullary P_{O_2} in experimental animals.[119 144] Furthermore, low urinary P_{O_2} during and after human CPB is associated with postoperative AKI.[144–148]

Conclusions

Perioperative hypotension is poorly defined but appears to be common and strongly associated with poor patient outcome, including acute kidney injury. The kidney is at risk because the lower limit of autoregulation of renal blood flow is higher than that of cerebral blood flow. Multiple mechanisms render the renal medulla particularly susceptible to ischaemia and hypoxia during the perioperative period. The susceptibility of the medulla to such injury probably makes a major contribution to incident postoperative acute kidney injury. Thus, a major barrier to progress is the lack of validated methods to monitor regional-kidney perfusion and oxygenation during the perioperative period. Uncertainty remains regarding (i) optimal targets for MAP in the perioperative period, (ii) whether intervening to increase MAP is actually beneficial, and (iii) the best therapeutic approach to prevent or treat perioperative hypotension. Adequately powered clinical trials are required to address this uncertainty. There is also an unmet need for pharmacological interventions to protect the kidney from the deleterious effects of perioperative ischaemia and hypoxia.

Authors' contributions

Narrative review development: YRL, RGE
Writing of paper: YRL, RGE
Creation of tables and figures: YRL, RGE
Provided intellectual input and clinical perspectives on the impact of conventional interventions on renal haemodynamics and function: CNM, RB
Review and approval of paper: all authors.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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