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Chronic renal disease in dogs and cats: anaesthesia considerations

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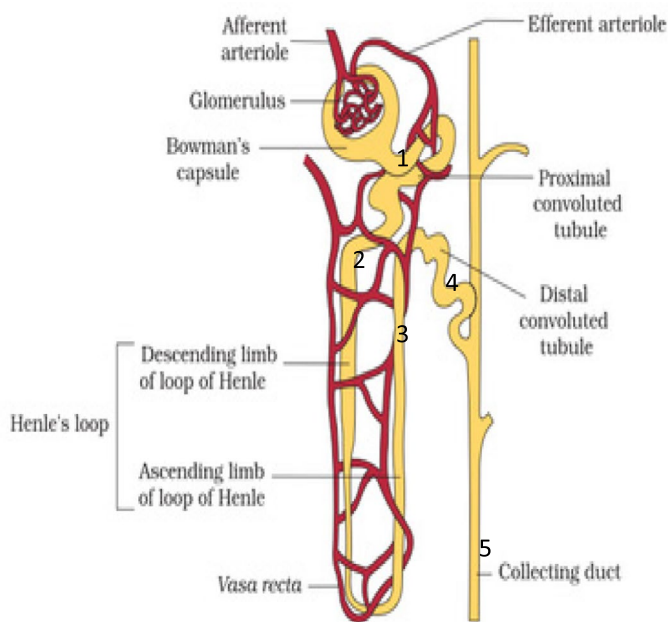
ABSTRACT: Chronic Kidney Disease (CKD) is a common diagnosis in the small animal population. In the UK, 3.6% of cats may experience CKD and renal disorders were the most common cause of mortality in cats over 5 years of age. In dogs, the reported prevalence of CKD is 0.37%, with a median (95% Confidence Interval) survival time from diagnosis of 226 (112–326) days. This article will review the main concepts of renal physiology and discuss considerations when anaesthetising a dog or a cat with CKD.

Keywords: anaesthesia; cats; chronic kidney disease; dogs

The kidney plays a fundamental role in maintaining fluid and electrolyte balances, as well as removing nitrogenous waste. Other functions of the kidney include: facilitating erythropoiesis via secretion of erythropoietin, vitamin D activation, maintaining acid–base balance, elimination of drugs by filtration/secretion, and maintaining blood volume via anti-diuretic hormone, also known as vasopressin. Nephrons, the functional unit of the kidney, are mainly concentrated in the cortex: approximately 190,000 nephrons are present in the cat and 430,000–580,000 in the dog. For this reason, about 90% of the renal blood flow (RBF) is directed to the cortex while the remaining 10% goes to the medulla. In total, the kidney receives approximately 20% of the cardiac output (Qt).

Glomerular filtration rate (GFR) describes the volume of fluid filtered by the glomerular capillaries every minute; it equates approximately to 1–4 ml/kg/minute. However, only a small amount of such volume will be eliminated as urine. Reabsorption, concentration or dilution in the proximal tubules, loop of Henle and distal tubules will determine the final urine volume (**Figure 1**), which is approximately 20–100 ml/kg/24 h in dogs and 10–20 ml/kg/24 h in cats.

The juxtaglomerular apparatus (JGA) is located within the nephron, adjacent to the glomerulus, between the efferent and afferent arteriole (**Figure 1**). It is composed of three types of specialised cells: macula densa, juxtaglomerular cells and extraglomerular mesangial cells. The JGA is responsible for activation of the renin-angiotensin system (RAS) following β_1 -stimulation, decreased renal perfusion, decreased Na^+ and Cl^- concentration – often due to a decrease GFR – at the macula densa. The RAS regulates RBF and GFR, adjusting the vascular tone of the afferent and efferent vessels (autoregulation), which in turn affects the filtration pressure (**Figure 2**). Renin, released from the JGA, facilitates the conversion of angiotensinogen, released by the liver, to angiotensin I, which is subsequently converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE) found in the lungs. Angiotensin II constricts the afferent and efferent arterioles reducing RBF and GFR. Catecholamines are the major hormonal regulator of RBF, with epinephrine and norepinephrine causing dose-dependent changes in RBF and GFR. Low doses increase arterial blood pressure (ABP) and decrease RBF with no net change in GFR; higher doses cause decreased RBF and GFR.



- To Excrete acid
1. Freely filter HCO_3^-
 2. Reabsorb the majority of filtered HCO_3^-
 3. Reabsorb some additional HCO_3^-
 4. Secrete H^+ (titrate filtered bases) and secrete NH_4^+
 5. Excrete acidic urine containing NH_4^+

- To Excrete Base
1. Freely filter HCO_3^-
 2. Reabsorb the majority of filtered HCO_3^-
 3. Reabsorb some additional HCO_3^-
 4. Secrete some HCO_3^-
 5. Excrete alkaline urine containing HCO_3^-

Figure 1. Nephron anatomy, including overall excretion of acids and bases. Adapted from Eaton and Pooler (2013).

While measurement of GFR (renal scintigraphy and iohexal plasma clearance) is the gold standard technique for assessing function of the kidneys, blood and urine analysis is more accessible and commonplace in practice, despite a lower sensitivity and specificity (Pressler, 2015). Furthermore, blood analysis might be useful to detect any concomitant diseases. An increase of blood urea nitrogen (BUN) and creatinine (Cr) can indicate presence of kidney disease. However, 60–75% of nephron function must be lost before such abnormalities can be detected (Pressler, 2015). Therefore, even patients with normal BUN and Cr could have a subclinical renal impairment. Further, pre-renal and post-renal causes might also be considered (Table 1).

In order to overcome the limitations of BUN and Cr analysis, a new biomarker SDMA (symmetric dimethylarginine) is being utilised to evaluate GFR. This is a methylated amino acid that has shown to be more sensitive than Cr for detecting a decrease in GFR in both dogs and cats, and is available to practitioners via IDEXX laboratories (Hall, Yerramilli, Obare, & Jewell, 2014; Nabity et al., 2015).

Urine specific gravity (USG) indicates the ability of the kidney to concentrate urine. Normal USG is 1.015–1.045 in dogs and 1.035–1.060 in cats (Osborne, Finco, & Low, 1983). Urine concentrating ability is often lost before azotaemia is detected in

dogs, but not in cats. Proteinuria is considered the hallmark of CKD in both dogs and cats, especially considering the poor sensitivity of blood BUN and Cr (Grauer, 2005). Once proteinuria is found on dipstick this can be verified and quantified by analysing the urine/creatinine ratio (UP/Cr), which is also an early indicator of early renal disease in dogs (Lees, Jensen, Simpson, et al., 2002; Grauer, Oberhauser, Basaraba, et al., 2002; Vaden, Jensen, Longhofer, & Simpson, 2001). A persistent increase in UP/Cr between 0.2 and 0.5 is classified as borderline proteinuria, while an UP/Cr ≥ 0.5 is considered significant proteinuria and is indicative of renal disease (Lees, Brown, Elliott, Grauer, & Vaden, 2005). Other biochemical abnormalities that can be detected in presence of CKD include hyperphosphataemia and hypoproteinaemia. While hyperphosphataemia is caused by the kidney's inability to excrete phosphate, hypoproteinaemia is caused by an increased renal loss due to glomerular damage and decreased reabsorption via the tubular epithelial cells (protein-losing nephropathy). Metabolic acidosis and hypokalaemia are also commonly associated with CKD; therefore, electrolytes and acid–base status should be assessed (Sparkes et al., 2016).

Non-regenerative anaemia is often concomitant to CKD. The aetiology is multifactorial and includes: a lower production of erythropoietin, a hormone secreted by the kidney that stimulates red blood cell

production; bone marrow suppression; gastrointestinal blood loss because of gastrointestinal ulceration/bleeding; and shortened red blood cell survival time (Macdougall, 2007). Anaemia decreases the arterial oxygen content and therefore oxygen delivery to organ and tissues. In case of severe anaemia (packed cell volume $< 20\%$), packed red blood cell or whole blood transfusion should be considered before and/or during anaesthesia, especially if peri-operative bleeding is expected.

Hypertension (SAP > 150 mmHg) can be classified as primary (idiopathic) or secondary; primary is the term used when there is no underlying disease; whereas secondary is a result of a disease process or drug therapy (Taylor et al., 2017). The pathogenesis of the secondary hypertension in CKD is not fully understood; however, sodium and water retention along with the activation of both the RAS and sympathetic nervous systems are fundamental for its development in humans. Cats with secondary hypertension due to CKD respond to treatment with amlodipine (a calcium channel blocker causing vasodilation), which suggests increased vascular tone may be particularly important in this species (Elliott, Barber, & Syme, 2001). Enalapril (an ACE-inhibitor) can be used to treat hypertension in dogs with CKD (Brown et al., 2003; Grauer et al., 2000). The reported prevalence of hypertension in patients with CKD ranges

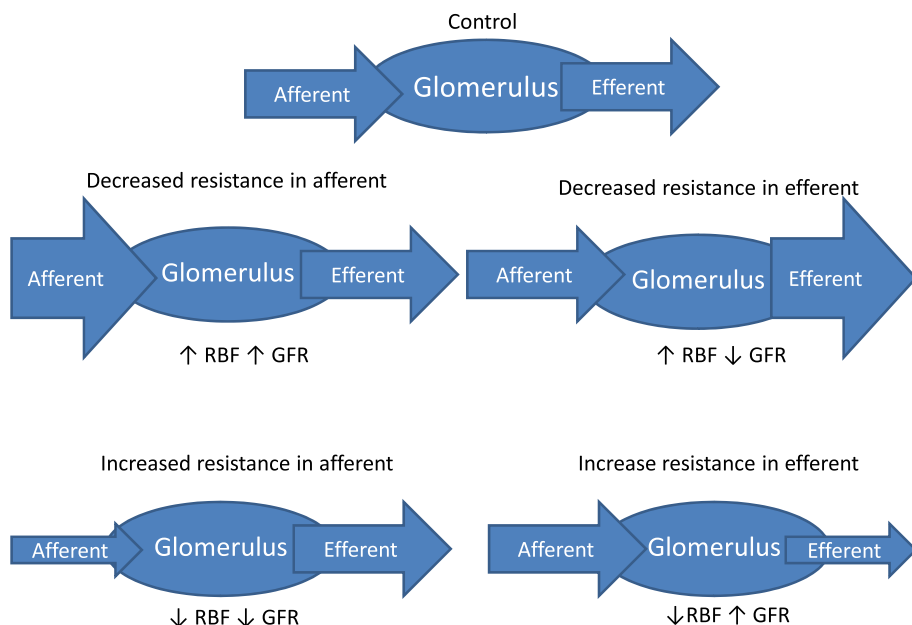


Figure 2. Glomerular blood supply and effect of vasoconstriction and vasodilation on renal blood flow (RBF) and glomerular filtration rate (GFR). Adapted from DiBartola (2006).

Table 1 Classification and main reasons for developing azotaemia.

Category	Causes	Disease/Condition
Pre-renal Azotaemia	Decrease kidney perfusion	Dehydration / hypovolaemia
		Heart disease
		Shock
		Addison's disease
Renal Azotaemia	Disease affecting the parenchyma	Infection
		Ischemia
		Toxins
		Congenital abnormalities
		Polycystic kidney disease
Post-renal Azotaemia	Urine excretion impairment	Ureter obstruction
		Urethral obstruction
		Ureter/urethral bladder/bladder rupture

Adapted from Paddleford (1988).

between 19–65% in cats and 9–93% in dogs (Brown et al., 2007). According to the International Renal Insufficiency Society (IRIS), it is possible to stage the severity of CKD in dogs and cats knowing the animal's ABP, urine protein levels and blood Cr concentration (www.iris-kidney.com).

The Doppler measurement has been suggested as the most accurate non-invasive technique to monitor ABP in conscious cats with studies showing good correlation between systolic readings when compared to invasive techniques (Taylor et al., 2017; Brown et al., 2007). However, high-definition oscillometry has recently become available (Martel et al., 2013). Guidelines

to standardise ABP monitoring in cats have been published by The International Society of Feline Medicine and can be accessed online (www.jfms.com). In dogs, both oscillometric and Doppler techniques are suitable (Haberman, Kong, & Brown, 2006).

Patients with CKD can be presented with a variety of clinical signs: polyuria (PU), polydipsia (PD), dehydration, disorexia or anorexia, weight loss, muscle wastage and depression; the latter is mainly associated with uraemia (Bartges, 2012). Prior to general anaesthesia (GA), hydration status should be assessed and corrected along with any electrolyte and/or acid–base imbalances. Patients with CKD are

potentially more sensitive to sedatives and anaesthetic agents especially in the presence of hypoproteinaemia and uraemia. The unbound pharmacologically active fraction of drug increases in the presence of hypoproteinaemia, potentially potentiating its effect. Furthermore, uraemia affects the ability of albumin to bind anaesthetic drugs, thereby exacerbating the phenomenon further. Uraemia also increases the permeability of the blood–brain barrier, facilitating the passage of sedatives and anaesthetics to the brain (Garcia, 2016). Moreover, in the presence of a depressed mental status common in a debilitated patient, anaesthetics can be easily overdosed.

When planning an anaesthetic technique it is important to understand that there is no drug absolutely contraindicated in patients with CKD; further, medications should be chosen considering the cascade. If an animal is debilitated and depressed, a relatively long-acting opioid alone (e.g. methadone) may be sufficient as pre-anaesthetic medication to reduce stress and provide analgesia with minimal cardiovascular effects. The type of pre-anaesthetic opioid should be chosen depending on the procedure to be performed. In the case of non-painful procedures, butorphanol could be preferred as it has more profound sedative effects compared to methadone and buprenorphine in dogs and cats, respectively (Bhalla, Trimble, Leece, & Vettorato, 2017; Trimble, Bhalla, & Leece, 2014). In livelier or fractious animals, the addition of a sedative agent may be required even to insert an intravenous cannula. Acepromazine (0.01–0.03 mg/kg, IM) could be combined with an opioid. However, acepromazine can cause vasodilation and this could result in hypotension (MAP < 60 mmHg), especially if the animal affected by CKD is relatively dehydrated or hypovolaemic. This side effect could be aggravated by the administration of a volatile anaesthetic (e.g. isoflurane). Despite this, it has been shown that RBF and GFR are maintained in healthy dogs despite systemic hypotension (Boström, Nyman, Kampa, Häggström, & Lord, 2003). Nevertheless, ABP should be monitored and treated as necessary. Alpha-2 agonists (medetomidine and dexmedetomidine) could also be combined with an opioid as pre-anaesthetic medications. Despite alpha-2 agonists reducing Qt, vital organ blood flow is maintained because of considerable redistribution and reduction of Qt to arteriovenous anastomoses and skin (Lawrence, Prinzen, & de Lange, 1996). Further, alpha-2 agonists produce preferential

vasoconstriction of the efferent arterioles; therefore, GFR is maintained or increased (Grimm et al., 2001; Saleh et al., 2005; Winte, Miles, & Riedesel, 2011). In cats with CKD, concomitant hypertrophic cardiomyopathy and left ventricular out-flow obstruction, an alpha-2 agonist may be considered (Lamont, Bulmer, Sisson, Grimm, & Tranquilli, 2002).

Pre-oxygenation prior to induction of GA is recommended especially in anaemic patients, in presence of concomitant lung disease or expected difficulties in achieving tracheal intubation. Either propofol or alfaxalone can be administered to induce anaesthesia. However, as a general rule, the administration should be performed slowly (within 60–90 s) in order to avoid overdose, more pronounced cardiovascular effects and apnoea. Especially when using alfaxalone, dilution of the drug to obtain a 0.25–0.5% solution could be useful to decrease the induction dose (Leece & McMillan, 2012). To further decrease the dose of GA necessary to induce anaesthesia a benzodiazepine (i.e. midazolam) and/or a short-acting opioid (i.e. fentanyl) could be used as co-inductors (Covey-Crump & Murison, 2008; Robinson & Borer-Weir, 2015). Ketamine is not contraindicated for induction of GA in animals with CKD. However, repeated boluses or infusion of ketamine might result in accumulation and prolonged effect due to impaired renal excretion. In dogs, ketamine is metabolised by the liver and nor-ketamine, the active metabolite produced, is excreted in the urine. In cats, ketamine is excreted unchanged by the kidney.

Anaesthesia can be maintained with a volatile agent, such as isoflurane or sevoflurane, both licensed in dogs and cats. However, the dose-dependent vasodilation and the negative inotropic effect produced by volatile anaesthetic can result in systemic hypotension that can lower RBF and GFR (Weil, 2010). For this reason, ABP should be closely monitored and treated as necessary. Sevoflurane has been linked to fluoride toxicity leading to no-oliguric renal failure when administered with a low-flow technique and using a carbon dioxide absorber in rats; however, this phenomenon has not been demonstrated in cats or dogs (Baden & Rice, 2000; Stoelting, 1999). Nitrous oxide could be beneficial reducing the minimum alveolar concentration of volatile anaesthetics providing analgesia, and counteracting the vasodilation caused by other volatile anaesthetics via sympathetic stimulation (Pypendop, Ilkiw,

Imai, & Bolich, 2003; Seddighi, Egger, Rohrbach, Hobbs, & Doherty, 2012). Total intravenous anaesthesia (TIVA) could also be considered in both dogs and cats. However, recovery could be prolonged, as excretion of the drug could be impaired. While either alfaxalone or propofol are suitable for TIVA and produce mild similar haemodynamic changes in healthy dogs (Ambros, Duke Novakovski, & Pasloske, 2008), prolonged propofol infusion can induce oxidative damage to feline red blood cells due to their inability to conjugate phenol, resulting in Heinz body anaemia and methaemoglobinaemia (Day, Andress, & Day, 1993). Therefore, alfaxalone may be preferred in cats even if there is paucity of information about its use in animals with CKD.

Systemic analgesic and/or local anaesthetic techniques should be implemented as part of a more balanced anaesthetic technique in order to reduce the amount of general anaesthetics necessary to maintain GA and therefore limit their negative impact on cardiovascular performance and on renal perfusion. Further, analgesia influences recovery quality, decreases the animal's stress, facilitates food intake and a rapid recovery. Systemic analgesics that can be used during surgery might be administered as boluses (i.e. fentanyl) or infusion (i.e. fentanyl, ketamine or lidocaine) depending on the length and invasiveness of the procedure (Matsubara, Oliva, & Gabas, 2009; Solano, Pypendop, & Boscan, 2006; Wilson et al., 2008). Loco-regional anaesthesia should be used whenever possible to block the transmission of a nociceptive signal to the spinal cord and decrease the risk of central sensitisation. Compared to neuraxial anaesthesia (spinal or extradural), peripheral nerve block might cause less vasodilation and hypotension (Campoy, Martin-Flores, Ludders, Erb, & Gleed, 2012), therefore having a minor impact on renal perfusion; however, the neuraxial administration of opioid (e.g. morphine) might be helpful producing long-lasting analgesia but limited cardiovascular effect (Troncy et al., 2002).

During anaesthesia, ABP should be monitored closely to ensure adequate renal perfusion. RBF and GFR remain relatively constant via a process of autoregulation, which is effective when mean ABP remains within 60–160 mmHg; in the presence of CKD it is advisable to maintain mean ABP between 70 and 80 mmHg (Green & Grauer, 2007). The expected anaesthetic time, the patient's clinical condition and the type of surgery to be performed should ascertain the

type of ABP monitoring implemented. Invasive monitoring should be preferred over non-invasive in cardiovascular-compromised animals, for prolonged procedures with anticipated risk of blood loss. Hypotension should be diagnosed and a goal-directed therapy approach undertaken (Figure 3).

Low doses of dopamine (1–3 µg/kg/minute) might exert a renal protective effect via renal vasodilation increasing RBF, GFR and urine output (UO). However, this effect is species-dependent. Dopamine receptors that control renal vasodilation have been demonstrated in dogs (Frederickson, Bradley, & Goldberg, 1985), but not in cats (Clark, Robertson, & Drew, 1991). While low doses of dopamine did not show a diuretic effect in cats (Whol, Schwartz, Flournoy, Clark, & Wright, 2007), higher doses (10 µg/kg/minute) produced a diuretic effect mediated by alpha-adrenergic receptors (Clark et al., 1991).

Body temperature should also be closely monitored during GA. Perioperative hypothermia is common in small animals; considering the suboptimal body condition score as a consequence of disorexia or anorexia, weight loss and muscle wastage, patients with CKD are at high risk of developing hypothermia. The side effects of hypothermia include: changes in the redistribution and metabolism of anaesthetic drugs due to a decreased metabolic rate and delayed recoveries; impaired blood coagulation; substantial increase in post-operative wound complications; post-operative shivering; and increased oxygen consumption (Davis, 2013a). Therefore, hypothermia should be prevented by minimising the anaesthetic time, maintaining acceptable environmental temperature, using active warming devices such as Bair Huggers™ or Hotdogs® along with blankets, and flushing the abdominal cavity with warm intravenous fluids. The availability of a multiparametric monitor could be helpful to maintain patient's homeostasis providing monitoring of electrocardiogram, ABP, capnography, pulse oximetry, body temperature and inspired and expired anaesthetic gas.

Intravenous fluid therapy (IVFT) should be used in order to support the circulating blood volume and, therefore, RBF. A balanced crystalloid solution (i.e. Lactated Ringer's Solution, LRS) can be used as it can also correct metabolic acidosis, if present. Despite the presence of potassium (4 mmol/l), LRS might need to be

supplemented with potassium chloride in the presence of hypokalaemia (Table 2).

In case of dehydration, IVFT should be started before anaesthesia; the amount of fluid to be administered should be calculated and replaced over 24 h using the following calculation:

$$[(\text{dehydration} \times \text{bodyweight}) + (\text{maintenance requirements} + \text{on-going losses})].$$

In normovolaemic animals, IVFT could be started at 4–6 ml/kg/h during anaesthesia; boluses of 5–10 ml/kg should be administered in case of hypotension secondary to hypovolaemia. In the presence of an arterial catheter, systemic pressure variability during mechanical ventilation can guide IVFT in fluid-responsive animals (Rabozzi & Franci, 2014). Colloid administration could be useful to maintain oncotic pressure in the case of hypoproteinaemia (1–2 ml/kg/h) or to expand the blood volume in the case of severe hypovolaemia (3–5 ml/kg bolus in dogs, 1–3 ml/kg in cats). Most colloids are excreted by the kidney so patients with severe kidney disease may be susceptible to volume overload. Hydroxyethylstarches have been implicated as a cause of acute kidney injury when used in hypovolaemic

Table 2 Potassium supplementation guide. Rate of IV infusion should not exceed 0.5 mmol/kg/hr.

Serum Potassium	Amount to add to 250ml 0.9% NaCl
< 2 mmol/l	20 mmol
2-2.5 mmol/l	15 mmol
2.5-3 mmol/l	10 mmol
3-3.5 mmol/l	7 mmol
3.5-5.5 mmol/l	5 mmol (minimum daily need in anorexic patients)

Adapted from Ramsey (2017).

humans and were therefore temporarily removed from the market (Mutter, Ruth, & Dart, 2013). However, lower molecular weight colloids (e.g. gelatins, licensed in dogs and cats) are available and could be used for fluid resuscitation in hypovolaemic patients or support of oncotic pressure in those with hypoproteinaemia (Davis et al., 2013b).

During surgery and the immediate post-operative period, UO decreases due to sympathetic activity, humoral regulation and activation of the stress response. Nevertheless, UO and USG measurement could be useful to guide IVFT in the post-operative period.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with

CKD is questionable. Inhibiting cyclooxygenases, NSAIDs decrease prostaglandin production from arachidonic acid. However, prostaglandins are essential in regulating RBF and vascular resistance of the renal arteriole, especially during periods of hypotension. Further, NSAIDs also inhibit leukotrienes, which also control RBF autoregulation and glomerular filtration pressure. Therefore, the administration of NSAIDs in animals with CKD undergoing GA and surgery should be avoided initially. However, NSAIDs may be suitable for post-operative pain management in selected cases (IRIS stage 1–2), if the animal is not dehydrated/hypovolaemic or hypotensive. There is no a safe NSAID; however, meloxicam has been administered off-licence in cats with CKD without reporting specific side

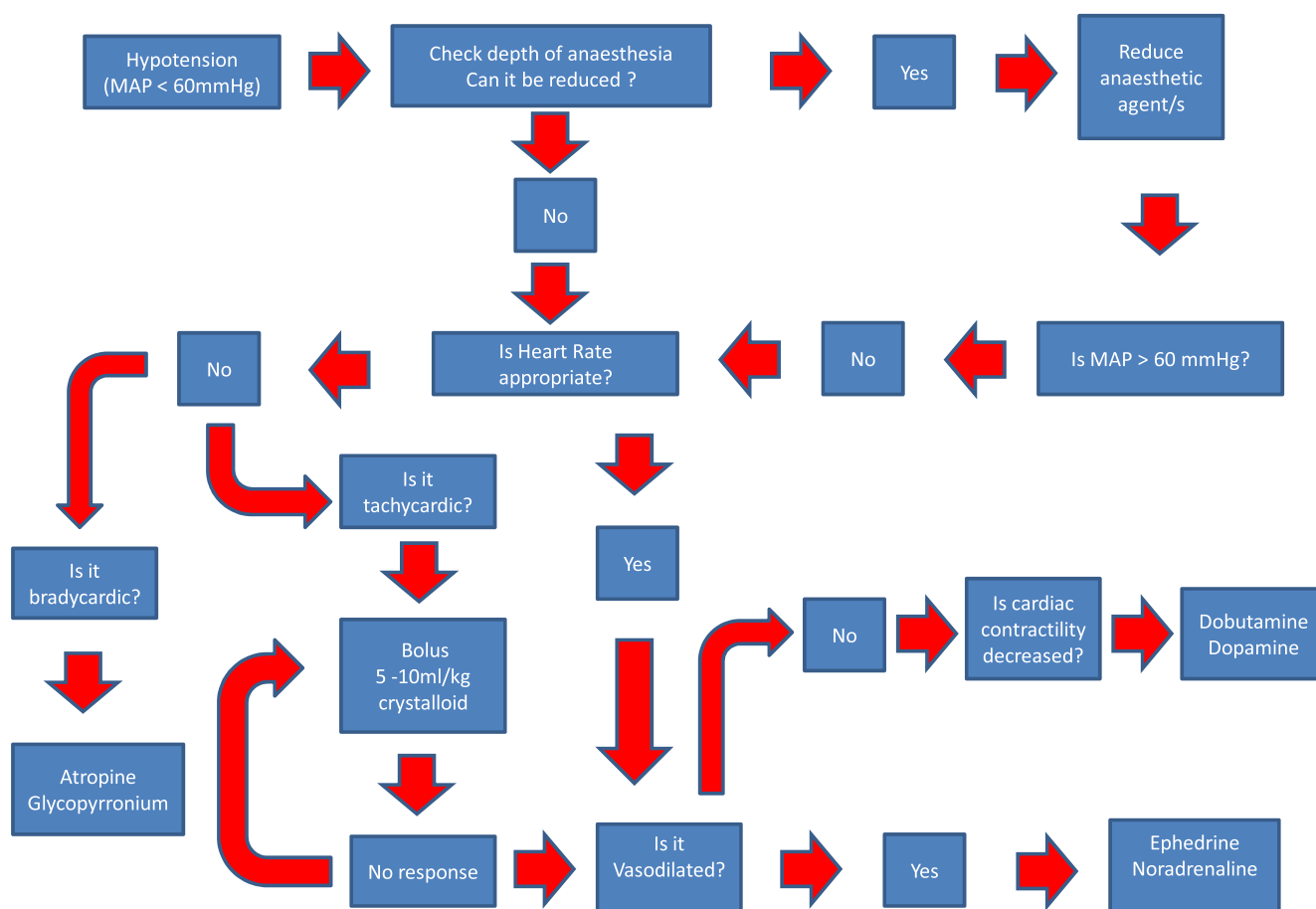


Figure 3. Algorithm to treat hypotension during anaesthesia

effects or worsening of the CKD (Gowan et al., 2012). Furthermore, low doses of meloxicam (0.02 mg/kg) in cats improved the quality of life of the animals (i.e. increase appetite), slowing the progression of CKD (Gowan et al., 2011). A further study looking at tepoxalin in dogs with CKD and osteoarthritis ascertained it may be used in IRIS stage 2 or 3 dogs alongside appropriate monitoring (Lomas, Lyon, Sanderson, & Grauer, 2013). Both carprofen and meloxicam have been shown to have minimal effects on renal function in healthy dogs when administered under GA (Boström, Nyman, Hoppe, & Lord, 2006; Ko, Miyabiyashi, Mandsager, Heaton-Jones, & Mauragis, 2000). If an NSAID is going to be prescribed, especially for long-term treatment, it may be beneficial to consider the concurrent use of a gastro-protectant medication, because NSAIDs can cause gastric ulceration/bleeding exacerbating potential ulceration cased in uraemic patients. The use of adjunctive analgesic therapies (i.e. gabapentin, amantadine, tramadol, pregabalin, amitriptyline) may also be considered.

In conclusion, there is no perfect recipe to anaesthetise patients with CKD. Medications should be chosen considering the cascade and their effect on the renal physiology. Pre-operative stabilisation, maintenance of normovolaemia, normotension, along with minimising the anaesthetic time and effective pain management are imperative to minimise further damage to the kidney.

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Multiple Choice Questions

1. How much renal blood flow is directed to the cortex?

- (a) 90%
- (b) 70%
- (c) 50%
- (d) 10%

2. Which of the following is a catecholamine?

- (a) Atropine
- (b) Angiotensin-converting enzyme
- (c) Epinephrine
- (d) Thyroxine

3. Kidney disease can be detected when which percentage of nephron function is lost?

- (a) 10-20%
- (b) 30-45%

(c) 60-75%

(d) 85-95%

4. Normal Urine specific gravity in the dog is considered as:

- (a) 1.010-1.025
- (b) 1.035-1.060
- (c) 1.075-1.090
- (d) 1.015-1.045

5. Which premedication drug may cause vasodilation and hypotension?

- (a) Acepromazine
- (b) Medetomidine
- (c) Dexmedetomidine
- (d) Buprenorphine

6. Uraemia increases the permeability of the blood brain barrier and facilitates the passage

of sedatives to the brain.

- (a) True
- (b) False

7. Which of the following constricts the afferent and efferent arterioles reducing renal blood flow and glomerular filtration rate?

- (a) Angiotensin I
- (b) Angiotensin II
- (c) Renin
- (d) Erythropoietin

8. Which of the following stimulates red blood cell production?

- (a) Angiotensin I
- (b) Angiotensin II
- (c) Renin
- (d) Erythropoietin

For the answers to the MCQs, please go to: <http://www.bvna.org.uk/publications/veterinary-nursing-journal>