Perioperative Management of the Hemodialysis Patient

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Abstract

Dialysis dependent chronic kidney disease (CKD) is an expanding problem for healthcare systems worldwide. The prevalence of end-stage renal disease (ESRD) has increased by 20% since 2000, and stands at 1699 per million people in the USA. ESRD is associated with an increased risk of cardiovascular comorbidity, increased severity of cardiovascular disease, and an adjusted all-cause mortality rate that is 6.4-7.8 fold higher than the general population. These patients may present electively or emergently for surgery related to, or remote from, the CKD. In any perioperative setting the haemodialysis dependent CKD patient represents a significant clinical challenge, and successful management of these patients requires effective cooperation and communication between nephrology, anaesthesia, and surgical staff. The ESRD patient's nephrologist will have the best knowledge of their medical history, co-morbidities, and future management goals, and may have been the clinician who instigated the referral for the surgery e.g. for parathyroidectomy, vascular access surgery, nephrectomy or renal transplantation. As such, they are in an ideal position to contribute to, or coordinate, early preoperative medical optimisation of the patient and also to provide advice during postoperative recovery and rehabilitation. In this article we provide an overview of some of the key aspects of managing these patients successfully during the perioperative period. We propose the integration of cardiopulmonary exercise testing and cardiovascular optimisation into the care of these high-risk patients, and provide an overview of the importance of maintaining microvascular perfusion and the role of viscosity in preserving the capillary perfusion network.

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Dialysis dependent chronic kidney disease (CKD) is an expanding problem for healthcare systems worldwide. The prevalence of end-stage renal disease (ESRD) has increased by 20% since 2000, and stands at 1699 per million people in the USA (1). ESRD is associated with an increased risk of cardiovascular comorbidity, increased severity of cardiovascular disease (2), and an adjusted all-cause mortality rate that is 6.4-7.8 fold higher than the general population (1). These patients may present electively or emergently for surgery related to, or remote from, the CKD. CKD is an independent risk factor for postoperative death and cardiac events (3) and successful perioperative management requires effective cooperation and communication between nephrology, anaesthesia, and surgical staff. In this article we provide an overview of some of the key aspects of managing these patients successfully during the perioperative period. We attempt to take the reader beyond the basic considerations to stimulate discussion around the integration of cardiopulmonary exercise testing and cardiovascular optimisation into the care of these high-risk patients, and to provide an overview of the importance of microvascular perfusion, particularly the role of blood and plasma viscosity in preserving the capillary perfusion network.

1. Preoperative medical optimisation of the dialysis patient

ESRD is a multisystem disorder. Cardiovascular disease remains the most frequent cause of death in ESRD patients, the largest single cause being fatal arrhythmias. The high rate of

associated multisystem comorbidity (Table 1) and the clinical effects of ESRD mandate a careful and systematic approach to preoperative preparation. The main features of such an approach include:

a) **Dialytic correction of metabolic status**
Hemodialysis adequacy is extremely important in the perioperative period and cannot be assumed simply from the patient's biochemical results e.g. blood urea and creatinine levels, or by relying on the absence of uremic symptoms. Dialysis dose can be determined using estimation of the volume of blood cleared during a treatment, the so-called "Kt/V". National and international standards exist (5) to define the target values for these measures, for example a minimum adequate treatment Kt/V of 1.2 for three times weekly dialysis, with a target dose of 1.4 per dialysis. It remains unclear whether achieving dialysis adequacy above the normal target levels (i.e. more intensive dialysis) improves surgical outcomes. It should be noted that dialysis dosing is based on fractional removal of toxins, regardless of any (largely unmeasurable) differences in their rate of production. The latter may well be increased in the often catabolic perioperative setting.

b) **Management of anaemia**
Loss of erythropoietin secretion as CKD progresses is the major factor that results in anaemia in the vast majority of HD-dependent ESRD patients if they remain untreated. This diminishes aerobic capacity and quality of life (6), as well as potentially aggravating myocardial dysfunction in susceptible individuals. Therapy with iron supplementation (e.g. intravenous iron) and erythropoietic stimulating agents (ESAs) currently target a haemoglobin concentration of between 11-12 g/dL (hematocrit 33-36%) (7). If reduction in the need for perioperative transfusion is desired, this target can be increased preoperatively by careful titration of ESA dose, although this will take a number of weeks to achieve. It should also be noted that there are concerns over adverse outcomes when using higher ESA doses to achieve haemoglobin levels above the above targets on a longer-term basis (8). The ESA dose may also need to be increased postoperatively to allow correction of surgery-induced anaemia and to overcome the generated inflammatory response, which induces erythropoietin resistance. In this setting iron repletion should also be optimized to facilitate the response.

c) **Tailoring of blood pressure and heart failure treatment**
Hypertension is common in hemodialysis patients and good control should be achieved to minimise perioperative instability. Management will include achieving the correct dry weight with optimisation of fluid removal, adjusting the dose of antihypertensive drugs, or adding additional agents. Intradialytic or postural hypotension is another common issue in hemodialysis patients, contributed to by excessive or too rapid fluid removal on dialysis, myocardial dysfunction, aggressive antihypertensive regimens, infection, pericardial effusion, exaggerated peripheral vasodilatation (worsened by anaemia) and abnormal sympathetic function (e.g. autonomic neuropathy). The cause should be sought and treated where possible (e.g. midodrine for intradialytic hypotension). Diastolic hypotension is an under-appreciated contributor to adverse cardiovascular outcomes (9). Heart failure medication should be tailored to optimum effect in the weeks before surgery with decisions regarding drug administration during the immediate preoperative period made in consultation with the anaesthesiologist or, if available, using agreed local protocols. In general, angiotensin converting enzyme inhibitors and angiotensin receptor

blockers are omitted on the day of surgery because of the risk of significant hypotension at induction of anaesthesia.

d) **Blood glucose control**

In the diabetic patient, therapeutic regimens should be tailored for best control of blood glucose, while also minimising the risks of hypoglycaemia. During the perioperative phase, hospital protocols or an individualised management plan should be used to ensure safe glucose levels, generally considered to be target levels < 180 mg/dl or 10 mmol/L (10-11). This may necessitate early involvement of specialist diabetic services**.** The targeting of much tighter glucose control is associated with increased risk of hypoglycaemia and adverse events and is not currently justified (12).. Hypoglycemia is a particular risk in this setting in patients treated with glyburide, an agent best avoided in dialysis patients.

Patients who have not been formally diagnosed with diabetes should also be assessed for hyperglycemia, since surgical stress may unmask and aggravate glucose handling problems in those with non-insulin dependent diabetes and also lesser degrees of glucose intolerance. Dialysis patients are also at increased risk of hypoglycaemia with fasting

e) **Calcium, phosphate and parathyroid hormone management**

Disorders of mineral metabolism are universal in ESRD patients and include reductions in Vitamin D and elevations in phosphate and parathyroid hormone. These abnormalities are associated with increased mortality risk, although it is unclear if they are causative, or whether treatment results in reduction of this risk (13). Medical management includes the use of phosphate binders and Vitamin D analogs, although achieving recommended treatment targets is difficult (14).

Rates of parathyroidectomy have increased again from 2005 through to 2007 after a previous decline (15). The so-called 'hungry bone syndrome' affects between 13 and 30% of parathyroidectomy patients. It consists of significant, symptomatic (tetany or seizures), and often prolonged hypocalcaemia, most often in patients with pre-existing bone disease and chronically raised bone reabsorption rates. In patients undergoing parathyroid/thyroid surgery with significant parathyroid hormone levels (typically > 800 pg/ml), the nephrologist may choose to prescribe high doses of calcitriol in the week running up to surgery to reduce the risk of this complication. Postoperative calcium and phosphate levels should be closely monitored. Hyperkalaemia is not uncommon in dialysis patients post parathyroidectomy, occurring in 80% of patients in one series (16) although the mechanism is not understood.

f) **Fluid and electrolyte status**

Close attention should be paid to establishing the correct 'dry weight' for the patient, i.e. the weight at which they are euvolemic. If the patient is above their dry-weight preoperatively, they risk pulmonary oedema and poorly controlled hypertension perioperatively and poor tissue healing postoperatively.. If under their dry weight they may become profoundly hypotensive during anaesthesia, which will be exacerbated by blood loss. It is usual to target low normal potassium levels going into surgery. Blood sampling in the very early post-dialysis period may return very low serum potassium values; these unequilibrated levels sometimes lead to inappropriate potassium repletion.

g) **Nutritional status**

Malnutrition is common in ESRD patients receiving hemodialysis and the pathogenesis is complex. Under-dialysis leads to anorexia and abnormalities in taste which impact

dietary nutrition intake. Increasing dialysis adequacy offers a realistic prospect of improving nutritional intake. Some of the other factors involved ESRD-related malnutrition include;

- restrictions in diet and fluid which reduce the calories available and make food less attractive
- medications which impair absorption of nutrients, bowel function and/or appetite
- loss of nutrients during hemodialysis
- dialysis induced catabolism
- chronic inflammation

Poor nutrition reduces tissue repair and should be corrected to minimise the risk of wound infection or dehiscence. In the case of elective surgery, there should be adequate time to involve a dietician, increase dialysis adequacy, and improve nutritional intake prior to surgery. In cases where this is not possible via the enteral route, parenteral nutrition (TPN) can be used to supplement or replace oral intake, and can be administered during dialysis sessions. Some patients whose taste and appetite are impaired despite optimal dialysis will tolerate nocturnal enteral feeding via a nasogastric tube.

h) **Haemodialysis vascular access**

This is often described as the patient's 'lifeline'. The nephrologist will communicate with other involved clinicians to stress how the access should be maintained, cared for, and used, and to discuss possible problems associated with it. For example, if the patient has a known central venous stenosis, this anaesthetist and surgeon should be informed as it may have implications for their practice or the planned procedure. As general rule, haemodialysis catheters should not be used for purposes other than dialysis (e.g. blood sample, CVP monitoring, drug administration) except in an emergency. An AV access may be at risk for thrombosis from procedure-associated hypotension. Access function should be checked as part of the post-operative evaluation.

i) **Issues relating to renal transplantation**

The first issue here relates to the "on-call" status of the patient awaiting transplant. In most cases, these patients will need to be suspended from the on-call list until they have recovered from their surgery. For some, the planned surgery will allow the patient to go on-call for the first time. The responsibility for coordinating this process lies with the nephrologist. A second issue relates to perioperative blood product administration. Transfused blood may cause an immunological response in the recipient, potentially making it more difficult for them to receive a renal transplant in the future. Nephrologists may ask for selected patient groups to receive HLA matched blood in attempt to reduce the risk of subsequent immunological issues. The availability of HLA matched blood will require close collaboration with the local blood transfusion service in advance of surgery. Patients who are on-call for transplant who receive blood transfusion perioperatively require follow-up blood sampling post-transfusion to assess antibody changes.

j) **Logistical issues relating to perioperative provision of haemodialysis**

The location and timing of dialysis need to be considered. The hospital where the surgery is to be performed may not have an on-site hemodialysis unit, or this unit may not be inside the main hospital building. In these scenarios, special arrangements will need to be made to provide hemodialysis when it is required. For example, in hospitals without chronic hemodialysis units, the patient may need to receive a period of renal replacement

therapy in a critical care unit that offers this therapy for acute kidney injury patients until they are stable enough to transfer to a different site for intermittent hemodialysis. It is important to ensure that the patient's fistula is properly maintained during this period of time. In most cases it is preferred that dialysis is carried out on the day before surgery to minimise any risks from anticoagulation and from unresolved fluid or electrolyte shifts. Dialysis may also be needed in the immediate preoperative period if there is a particular problem with fluid or potassium control.

k) **Infection control issues**

ESRD patients are at increased risk of bacterial colonisation and infection by virtue of altered neutrophil and monocyte function, impaired lymphocyte activation or number, cytokinemia and abnormal pathogen recognition (17). This risk naturally extends to organisms such as MRSA (methicillin-resistant Staphylococcus aureus) (18), VRE (vancomycin-resistant enterococcus) and ESBL (Extended-spectrum beta-lactamase producing gram-negative organisms). Colonisation or infection with these organisms may have implications for the location where the patient is nursed or receives their dialysis. It may also impact on the order of the operating list, which operating room is used and what surgical antimicrobial prophylaxis is required. It is therefore critical that information on infection status be communicated to the surgical and anaesthetic teams involved, and that clinicians appreciate the increased susceptibility of these patients to infection.

l) **Dialysis and emergency surgery**

In some instances, it is not possible to undergo preoperative dialysis (as with a ruptured abdominal aortic aneurysm or for surgery to salvage a non-functional vascular access for hemodialysis). In these cases medical management of hyperkalemia may be required with close intraoperative monitoring by the anaesthesiologist and a plan to commence dialysis as soon postoperatively as is judged safe. Although hemodialysis patients running chronically elevated potassium levels may be less susceptible to hyperkalemia-induced cardiac toxicity than previously normokalemic patients (19), this cannot be guaranteed. It is also often assumed that preoperative fasting reduces the likelihood of hyperkalemia; it does not. The hormonal response to fasting favors the shift of potassium from the intracellular to the extracellular space

m) **Reduction in bleeding risk**

HD-dependent ESRD patients are at increased risk of perioperative bleeding. Chronic uraemia (or more accurately the chronic presence of uremic toxins) is associated with (a) defective platelet granule release of serotonin and thromboxane A2 (activation defect), (b) reduced activity of platelet surface receptors (aggregation defect), and (c) reduced von Willebrand factor activity (adhesion defect) (20-21). Anaemia alters the normal pattern of flow in vessels, where red cells are predominantly found centrally and platelets are thrust outward towards the vessel wall.

ESRD patients may be taking medications such as aspirin and clopidogrel that reduce platelet aggregation. They will also be receiving prophylaxis against deep venous thrombosis (DVT) in the perioperative period, generally in the form of unfractionated heparin. Low molecular weight heparin, popular for DVT prophylaxis in Europe, undergoes predominantly renal excretion and accumulates in ESRD, increasing bleeding risk. If used, doses should be significantly reduced, and consideration given to monitoring of anti-Xa activity (22). Although low-dose aspirin has been safely continued

through the perioperative period, clopidogrel should be discontinued 7 days prior to surgery unless there are specific indications for its use.

Adequate dialysis and uraemia reduction in the perioperative period will help improve platelet function (heparin-free dialysis close to time of surgery). Administration of a 0.3 micrograms/kg dose of Desmopressin (dDAVP) releases factor VIII and von Willebrand factor from the endothelium (23), and this action lasts for between 4 and 12 hours. It should be noted that tachyphylaxis occurs. Factor replacement through administration of cryoprecipitate also shortens bleeding time in uremic patients, the effect lasting 12-24 hours. A positive effect of conjugated estrogen administration (0.6 mg/kg daily for 5 days) has also been found, commencing around 24 hours after the first doses and peaking after 5-7 days of therapy. In circumstances where other techniques have failed, tranexamic acid may be effective, although it accumulates in renal failure (21).

Preoperative anaesthetic assessment

In addition to the acquisition of basic patient data and clinical history, the key role of preoperative assessment is to identify correctable problems and institute therapy that optimizes the patient's organ function prior to the surgical and anaesthetic challenge. The preoperative detection of cardiac ischemia risk is the most frequently discussed area. Scores such as the Revised Cardiac Risk Index (RCRI) (24) (Table 2) go some way towards identifying the higher risk patient. Traditional assessment of cardiac risk and ischemia has been the subject of several excellent reviews and guidelines (25-26) and will not be reviewed here. We would, however, like to highlight the potential utility of an integrated assessment of cardiopulmonary fitness in the detection of patients at higher risk of perioperative mortality or morbidity, and briefly review the integrated preoperative cardiopulmonary exercise test (CPET) for functional status assessment.

Identifying patients at risk of poor outcomes – functional capacity and oxygen delivery

Major surgery is associated with endocrine changes and a systemic inflammatory response. The result of these changes is an increase in intraoperative, and especially postoperative, oxygen demand and consumption. Ideally this demand is met through a rise in cardiac index and oxygen delivery and a parallel rise in oxygen extraction by the tissues (27).

Oxygen delivery depends on cardiac output and the oxygen content of blood, with the dissolved oxygen contributing only a small fraction to the delivered oxygen. Thus, an adequate haemoglobin concentration and haemoglobin saturation level are important, but alterations in cardiac index have the greatest impact on oxygen delivery. For some patients, especially those with heart failure, the rise in delivery that should accompany the change in demand cannot be provided by their cardiopulmonary systems without pharmacological support, and tissue hypoxia with metabolic failure ensues. Globally this may be detected by a rise in lactate level, a worsening base deficit, or a fall in mixed venous or central venous oxygen saturation (normally 70-75%). It should be remembered that regional perfusion might be severely deranged before these global measures change. Derangements in global oxygen delivery have been associated with poor outcome after major surgery (28). A critical part of perioperative management involves identifying these hypoperfusion-prone patients prior to surgery, and intervening to optimize their cardiac status, oxygen delivery and perfusion. Given the prevalence of cardiovascular disease in the HD-dependent ESRD population, these patients are very suitable targets for testing and investigation.

An increasingly utilized tool to evaluate functional capacity, oxygen demand, and delivery, is the

integrated cardiopulmonary exercise test (CPET), carried out using a stationary exercise bicycle or a treadmill. This test can provide valuable information on the causes of deficient oxygen delivery, and the exercise level at which this occurs. The methodology for this investigation has been reviewed elsewhere (29), but a number of relevant parameters are measured, one of the most quoted being the peak oxygen uptake and the so-called anaerobic threshold, the point at which oxygen delivery is insufficient to meet aerobic metabolic demands. Patients with an anaerobic threshold (AT) below 11 ml/minute/kg (or 11-14 ml/minute/kg with cardiac ischemia) are known to be at increased risk of poor postoperative outcomes after major non-cardiac surgery (30-31), and the test retains this discriminatory ability in the absence of cardiac risk factors. These high-risk patients should have their care optimized in a high-dependency or intensive care environment post-operatively (although some units admit such patients prior to surgery). It is important to differentiate between CPET to assess functional capacity, oxygen delivery, oxygen consumption, and postoperative disposition from conventional stress testing to detect inducible cardiac ischemia. These investigations are not directly interchangeable, despite the ability of CPET to detect myocardial ischemia.

Cardiovascular dysfunction in the hemodialysis patient

CKD not only increases the risk of cardiovascular disease, it also worsens the associated outcomes (32-33). Cardiac mortality is between 10 and 20-fold greater for HD-dependent patients than matched controls that do not have CKD (34). The most common cardiovascular issues in the CKD patient are arteriosclerosis-mediated hypertension, ischaemic heart disease, cerebrovascular disease, accelerated vascular and cardiac valvular calcification, impaired systolic and/or diastolic ventricular function (with concentric or eccentric left ventricular hypertrophy), and arrhythmogenic sudden cardiac death (35). The prevalence of these disorders increases with the severity of CKD, such that 32-34% of patients on dialysis for ESRD meet ECG or echocardiographic criteria for left ventricular hypertrophy (as do up to 80% of incident dialysis patients), 40% have symptomatic ischaemic heart disease (and likely many more are asymptomatic), 40% have evidence of cardiac failure, 32% have arrhythmia (36-37). These very likely place patients at higher risk of poor perioperative outcomes as has been shown for elderly patients with systolic ventricular dysfunction (symptomatic or asymptomatic) after vascular surgery (38).

The prevalence of heart failure continues to grow, as does the appreciation of the importance of heart failure with preserved ejection fraction, previously known as diastolic heart failure, which impacts adversely on ventricular filling and can lead to pulmonary edema at lower end-diastolic volumes (preload levels). Diastolic dysfunction is associated with increased risk of postoperative cardiovascular events and long-term cardiovascular mortality after vascular surgery (39).

Hemodynamic management of "high-risk" patients

High risk patients may be defined as those with an anaerobic threshold less than 11 ml/minute/kg, a Revised Cardiac Risk Index Score $\geq$ 3 points, or a predicted perioperative mortality of > 5%. There are two main approaches to this patient group:

1) The use of additional (more invasive) monitoring such as central venous pressure, invasive arterial pressure, or less commonly pulmonary arterial catheterization. In addition to the standard targets identified above, this approach is usually based on achieving and maintaining a given central venous (CVP) or pulmonary arterial wedge pressure (PAWP) as an index of adequate

fluid loading, with pressor or inotropic agents used if this approach fails to meet MAP goals. There are significant limitations in assessing intravascular volume status through CVP or PAWP, given the poor relationship between CVP or PAWP and the patient's fluid-responsiveness (40-41). Administration of anaesthetic drugs in high-risk patients can be associated with a significant reduction in cardiac output and blood pressure, and the use of predominantly vasoconstrictor agents like metaraminol or phenylephrine in this setting transiently supports blood pressure but further diminishes cardiac output and risks reduction in tissue oxygenation. In the absence of cardiac output monitoring this deficit may not be apparent to the anaesthetist, since mean arterial pressure targets have been met. If a decision is made to monitor cardiac index, a baseline pre-anaesthesia value is very important because simply achieving a rise from a post-induction nadir may not restore pre-anaesthesia levels and adequate O_2 delivery.

2) The use of techniques focused on hemodynamic optimization or "goal-directed therapy", specifically targeting defined cardiac function and oxygen delivery indices as well as maintaining a "safe" perfusion pressure. Intravenous fluids, inotropes, or vasopressors, are used to achieve these end-points, with increasing emphasis on goal-directed fluid therapy as core component (42). This model traditionally utilized the pulmonary artery catheter, but increasingly makes use of various additional monitors capable of assessing dynamic indices of vascular filling such as arterial waveform analysis to detect systolic pressure variation (SPV) or pulse pressure variation (PPV), which have better correlation with fluid-responsiveness than the static indices of CVP and PAWP (43) (although the patient should be in sinus rhythm and mechanically ventilated). It is also possible to study the variation in the plethysmographic signal from a pulse oximeter to infer the presence and severity of SPV and guide fluid therapy (44-45). Information on cardiac function may be obtained less invasively through interrogation of aortic blood flow by oesophageal Doppler techniques (46) or through arterial line-based pulse contour analysis and transpulmonary thermodilution, which also yields information on extravascular lung water levels and intrathoracic blood volume and global end-diastolic volume (preload) (47).

The literature on perioperative hemodynamic optimization generally focuses on maintaining normal or supranormal oxygen delivery indices through optimization of (a) intravascular volume and (b) cardiac index. These techniques assume adequate arterial oxygenation and haemoglobin concentration. The literature on hemodynamic optimization continues to spark debate, but there are several positive studies and meta-analyses suggesting improved short-term outcomes, organ impairment, and potential for reduced hospital stay in major abdominal surgery including high-risk patients (48-52), and these techniques may help avoid over- or under-hydration and the adverse effects that may result (53). There are, however, no studies focusing on perioperative hemodynamic optimization specifically in the ESRD population, and indeed these patients may be excluded from some trials. However, given the common cardiopulmonary comorbidities prevalent in the ESRD population, it is appropriate to consider such an approach in the high-risk ESRD patient.

Optimization in the presence of significant active cardiac ischemia

Hemodynamic optimization of patients with severe or unstable ischaemic heart disease requires an approach that takes account of the fact that (a) their drug therapy often concentrates on beta-blockade and reduction in cardiac oxygen consumption and (b) their major risk is critical cardiac ischemia or infarction. In these patients, optimization presupposes optimal cardiac

revascularization and avoids or minimizes the use of beta-agonist inotropes. Fluid optimization is achievable using the tools discussed above. In the presence of ventricular dysfunction, cardiac output and oxygen delivery may be supported through the use of alternative inotropic agents such as phosphodiesterase inhibitors (e.g. milrinone) or the novel calcium-sensitizing inotrope, levosimendan (54), and perioperative support with an intra-aortic balloon pump may be of use in emergent cases where pump function is poor and revascularization not feasible. This approach has not yet been rigorously investigated and is unlikely to be a topic for a large randomized trial.

Microvascular resuscitation and correction of tissue dysoxia

CKD is associated with endothelial dysfunction and microvascular perfusion abnormalities (55), related both to underlying comorbidities and specifically to CKD; these abnormalities are exaggerated during dialysis (56-57). Optimal perioperative management aims to maintain tissue perfusion and oxygenation, and as such requires an optimized or recruited microvasculature. Tissue oxygenation in critical organs such as the brain can be measured. Cerebral oxygen saturation is monitored by near-infrared spectroscopy (58). Cerebral desaturation is associated with a higher risk of postoperative cognitive impairment (59-60) and may occur despite adequate mean arterial pressure and global hemodynamics, being induced, for example, by inadvertent hyperventilation and the cerebral vasoconstriction that accompanies it. This insult should be avoided, where possible, in the CKD population who are already at increased risk of vascular-origin cognitive impairment (61). The technology to monitor absolute cerebral oxygen saturation is commercially available and is slowly emerging into non-cardiac perioperative and critical care. Given the position of the brain as the ultimate organ to be protected perioperatively, trials looking at the inclusion of cerebral saturation monitoring within optimization algorithms seem intuitive and desirable, but this area remains to be adequately investigated.

Most of the work done to date has involved macro-hemodynamics and been based on the assumption that targeting appropriate mean arterial pressure, cardiac output, and oxygen delivery necessarily equates to adequate tissue perfusion and oxygenation. In the context of relative anemia and hemodilution, two common perioperative issues in the ESRD patient with or without fluid optimization, it is useful to look to recent work on microvascular perfusion and functional capillary density to see if there are additional factors that we need to consider when we attempt to optimize tissue perfusion. This work has recognized (a) the critical role of blood viscosity in the maintenance of capillary density at tissue level – blood viscosity and shear stress act on the capillary endothelium and induce physiological nitric oxide (NO) release which increases capillary diameter and density (62) (b) the detrimental impact of arteriolar vasoconstrictors, predominantly the alpha-agonists, which maintain mean arterial pressure but induce pre-capillary vasoconstriction and actually reduce functional capillary density and perfusion (63) and (c) that the effect of reduced capillary density is further aggravated by tissue edema, which increases the capillary to cell diffusion distance.

Why is this relevant to the perioperative management of the ESRD patient? We have already acknowledged the incidence of pre-existing microvascular impairment in CKD, so these patients are starting off with a deficit. There is also a prevalent approach based around "permissive anaemia" in the perioperative period, ESRD patients perhaps entering surgery with haemoglobin concentrations of 11-12 g/dL and encountering transfusion triggers of around 7g/dL (in otherwise "well" individuals) to 8 or 9 g/dL (in the very elderly or patients with cardiovascular disease), extrapolated from the critical care environment, and we would like to stimulate research and discussion on the implications of this approach. Anaemia, aggravated by hemodilution with

crystalloids or low-viscosity colloids, reduces functional capillary density by failing to generate capillary NO release and so promoting vasoconstriction. An approach to transfusion based on detecting abnormal global measures of oxygenation such as lactate and mixed/central venous oxygen saturation may not be the most effective strategy, given that by the time these abnormalities occur, blood viscosity could already be low enough that capillary density has fallen.

There is, therefore, a balance to be sought between the beneficial effect of lower hematocrit on blood rheology and the detrimental effect of "viscosity failure" on perfusion. Indeed it has been suggested, based on animal studies of acute hemodilution and hemorrhage, that there may be an argument for a "viscosity trigger", a point at which fluid (generally viscous colloids, hyperoncotic solutions, or blood) administration is required to recruit the microcirculation at hematocrit or hemoglobin levels that would not otherwise represent the conventional "transfusion trigger" (64-65). Thus stored blood, although not immediately capable of full oxygen carriage, will improve tissue oxygenation through improvement in blood viscosity and functional capillary density (66). Similarly, tissue blood flow and oxygenation in severe anaemia will be better maintained if blood viscosity is supported (67). This is a new concept that will require further clinical investigation, but which provides a tantalizing glimpse into the direction that optimization might take for populations including HD-dependent ESRD. At present, tools to monitor functional capillary density and capillary recruitment, such as sidestream dark field imaging (68), are generally limited to clinical trials and not readily available to the practicing clinician.

Pulmonary hypertension and right ventricular dysfunction in the hemodialysis patient

One of the most significant abnormalities in ESRD is pulmonary hypertension (PH), although this often receives much less clinical attention than it deserves. PH may be present as a result of cardiac dysfunction or have developed de novo after formation of an AV fistula and/or commencement of hemodialysis (69). The incidence of PH in patients with ESRD and AV fistulae may be as high as 40% (70).

The pathophysiology of PH in end-stage renal disease may be related to uremia-induced endothelial dysfunction, as basal nitric oxide levels have been shown to be lower in hemodialysis patients with pulmonary hypertension compared to those without (71-72). This is thought to reduce the ability of the pulmonary vasculature to accommodate the increase in cardiac output derived from the AV fistula, and it has been suggested that PH should be specifically sought in patients scheduled for fistula formation, and the plan for fistula reconsidered in those who are identified as already having pulmonary hypertension (73). Another factor that may account for the high frequency of PH in this population is pulmonary injury resulting from chronic exposure to microbubbles originating in the dialysis tubing or filter (74).

Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients, with a 5-year survival rate of only 25% (69) compared to 39% for the overall HD population. It is interesting to note that both fistula closure and renal transplantation have been shown to reduce pulmonary artery pressures in hemodialysis patients with PH (71).

The presence of severe pulmonary hypertension should be determined pre-operatively as it will have a significant impact on the anaesthetic management of the patient. Management goals should centre on the avoidance of hypoxia, hypercapnia, acidosis and hypothermia as each of these factors will increase pulmonary vascular resistance. Right ventricular preload must be maintained as right ventricular underfilling, through ventricular interdependence, will lead to

septal shift and a reduction in left ventricular preload which will lead in turn to a reduction in cardiac output and hypotension/ischemia (75).

General aspects of intra-operative management

Aside from the impact of surgery and comorbidity, there are a number of general perioperative care issues to be considered in this patient population. Intravenous access and blood pressure monitoring should avoid the AV fistula arm. Patient identification armbands must not encroach on the fistula and compression of the fistula during surgery must not occur (76). In cases requiring central venous access, the subclavian approach has been associated with an increase in the rate of subclavian vein stenosis (77). This may become sufficiently severe as to prevent both the future use of the subclavian vein as well as the successful placement of an AV access in the ipsilateral arm (due to inadequate venous drainage resulting in marked arm swelling) Thus, it has been recommended that subclavian central venous access should be avoided. There are those who argue that improvements in central venous catheter technology and care, use of ultrasound guided insertion, and a reduction in central venous catheter associated infection, may result in a lower risk of stenosis although this remains to be studied.

Pharmacological issues and drug choices

Potential alterations in volume of distribution, protein binding, drug metabolism and excretion must be considered carefully before deciding upon a particular anaesthetic technique.

a) **Anaesthetic drugs**
   Propofol is an intravenous induction agent, which can also be administered by continuous infusion to maintain anaesthesia or sedation. The pharmacokinetics of bolus administration, and of maintenance infusion, do not seem to be markedly altered in ESRD patients (including those dialysed 12 hours prior to surgery) (78-79).

   Sevoflurane is a widely used inhalational anaesthetic agent that may react with carbon dioxide absorbents to produce a substance called Compound A, which is nephrotoxic in rat models (80). Although Sevoflurane is also biotransformed to release potentially nephrotoxic inorganic fluoride ions, it has been used in renal disease and dialysis-dependent ESRD patients and it appears to be safe, with serum inorganic fluoride levels and elimination rate no different than healthy controls (81-82).

   Patients with end-stage renal failure have below-normal levels of plasma cholinesterase. This results in a prolongation of action of the depolarising muscle relaxant suxamethonium (83) and the non-depolarising relaxant mivacurium (84)**.** A significant hyperkalemic response to suxamethonium is not observed in chronic renal failure provided the pre-operative potassium level is within normal limits (85).

   The non-depolarising muscle relaxant drug atracurium, and the stereoisomer cis-atracurium, undergo a process called Hofmann elimination which is independent of renal and hepatic function, making these agents useful neuromuscular blockers for the renal failure patient (86). In contrast, the clinical effects of the amino-steroid muscle relaxant drugs vecuronium and rocuronium are significantly prolonged in renal failure due to reduced clearance, the disease process causing ESRD, or the effects of other medications (87-89).

Sugammadex is a novel cyclodextrin that has been demonstrated to rapidly reverse neuromuscular blockade induced by rocuronium and vecuronium, even at depths of block where conventional reversal with acetylcholinesterase inhibitors would be ineffective (90). The resulting Sugammadex-rocuronium complex is excreted via the kidney, although clearance is obviously reduced (91). In a recent study of patients with renal failure, Sugammadex (2 mg/kg) rapidly reversed the neuromuscular blockade induced by rocuronium without any adverse effects (92); 10 of the 15 patients with renal failure in this study were undergoing dialysis. There is clearly a need for further studies of this novel reversal agent in much greater numbers of patients with renal failure to clarify its role in this setting.

b) Opioid analgesics

When considering perioperative analgesic requirements for HD patients it is important to recognise the effect of renal failure both on the clearance of both parent drug and its metabolites e.g. morphine and morphine-3 and morphine-6-glucoronides. The impact of CKD and ESRD on common opioid agents, and considerations for use, are outlined in Table 3. The mechanics of dialysis will also play an important role in deciding which opioid, if any, to utilize (93).

With its unique mode of metabolism by plasma non-specific esterases, intra-operative analgesia and prevention of haemodynamic responses in dialysis-dependent ESRD patients may be safely and reliably provided through infusion of remifentanil, a potent μ receptor agonist with a constant context-sensitive half time i.e. no effect site accumulation and a predictable offset of action which is independent of infusion duration, with no apparent increase in adverse effects (94-95). Although end stage renal failure prolongs the elimination half-life and reduces the central clearance of remifentanil, the clinical significance of these findings appears to be minimal (96). Naturally, intraoperative use of such an agent requires additional techniques to provide post-operative analgesia.

c) Non-steroidal anti-inflammatory agents (NSAIDs)

NSAIDs are often used in haemodialysis patients either to reduce cardiovascular risk (in the case of aspirin) or to help control chronic pain. A recent retrospective observational cohort study (97) randomly selected over 28,000 haemodialysis patients from The Dialysis Outcomes and Practice Patterns Study (DOPPS) to analyse aspirin prescription and outcomes. They found that aspirin prescription was not associated with an increased risk of gastrointestinal haemorrhage in these patients. This point has been debated (98) with calls for adequately powered prospective trials to clarify the risk of gastrointestinal haemorrhage in haemodialysis patients taking NSAIDs). Also of concern is the potential adverse effect of these agents on residual renal function, a risk that has not been well evaluated. A careful risk/benefit decision needs to be taken on an individual patient basis before deciding to prescribe NSAIDs to this patient group during and after surgery.

d) Use of regional and neuraxial anaesthesia and analgesia

Regional anaesthetic techniques have been used to aid creation of arteriovenous fistulae (99). In chronic renal failure patients with low bicarbonate values the onset of action of local anaesthetics may be delayed (100) and the duration of effect may be lower in these patients

perhaps due to low protein binding (101). Epidural analgesia has been successfully utilised for labour analgesia and caesarean delivery in the setting of end-stage renal failure (101) and for renal transplantation (102), and provides safe and effective post-operative analgesia after abdominal and thoracic surgery. Platelet number/function and coagulation profile should be checked before any regional technique is carried out in these patients, and drugs such as clopidogrel should have been stopped sufficiently in advance.

Bilateral transversus abdominal plane (TAP) blocks are used with increasing frequency to minimise opioid usage following abdominal surgery. They have been used as part of a balanced analgesic regime in patients undergoing renal transplantation. In a pilot study involving 20 patients TAP blocks were shown to reduce both intra and post-operative opioid consumption (103). Paravertebral block may be used to provide analgesia after thoracotomy or unilateral abdominal procedures such as nephrectomy.

Intravenous fluids

Careful consideration should be given to the type and quantity of fluid to be administered during surgery. This will be determined by the preoperative hydration status of the patient, duration of surgery and the estimated fluid losses occurring during surgery, along with dynamic preload measures if utilized. Overzealous administration of intravenous fluid risks tissue and pulmonary oedema (remembering that diastolic dysfunction is prevalent) whilst under administration risks haemodynamic instability and impairment of oxygen delivery. Large volumes of 0.9% saline solution may lead to hypernatremia and a significant hyperchloremic acidosis, although this can be corrected by dialysis. Solutions such as Hartmann's solutions (Ringer's) contain less sodium and less chloride, but some advocate avoidance since they contain some potassium. There is a wide range of colloid fluids on the market now, broadly breaking down into dextrans, gelatins, and (heta-)starches. Lower molecular weight starches have been shown to reduce the incidence of delayed graft function after renal transplantation compared to higher molecular weight versions (104), and are increasingly used as first line colloids.

Post-Operative Care

Whether or not to admit the patient to a high dependency or intensive care unit post-operatively will depend on the nature of the surgery and specific patient factors (determined at preoperative assessment) that may place them at higher risk of cardiorespiratory complications. Haemodialysis should ideally be delayed until the risk of fluid shifts and haemorrhage has fallen (some suggest at least 24 hours post-operatively) (76) and, depending on the nature of surgery, anticoagulation may need to be reduced or omitted. The re-establishment of postoperative dialysis will require close liaison with a nephrologist and a specific plan for this should be in place pre-operatively.

The immediate post-operative period will require close attention to fluid and electrolyte balance. As with intraoperative fluids, we tend to give a low background maintenance fluid infusion (taking into account native urine output and insensible losses) supplemented by bolus doses of crystalloid or colloid to maintain haemodynamic stability, and help reduce the likelihood of fluid overload. Electrolyte, urea and creatinine levels should be checked in the early postoperative period and as indicated thereafter.

A multimodal approach to postoperative analgesia should be employed. If the patient suffers from chronic pain he/she will have a higher analgesic requirement and should receive his/her usual analgesics supplemented by additional methods (e.g. regional technique) to cover for the acute surgical insult. In Europe, intravenous preparations of paracetamol are effective and beneficial in patients whose gastrointestinal function has not recovered. Combinations of local anaesthetic wound infiltration, nerve blocks or regional analgesia where the surgery is amenable to these, and regular paracetamol markedly diminish opioid requirements, which is a significant aim given the risk of accumulation of drug or metabolites. If a clinician determines that it is necessary to administer opioids such as morphine, the dose should be reduced and the patient should be carefully monitored. The use of intrathecal or single-shot epidural opioids provides good quality analgesia for up to 24 hours postoperatively, although there is little evidence on this approach in the ESRD population. Such patients are routinely monitored for respiratory depression even in the absence of organ impairment.

With regard to management of hypertension, ischaemic heart disease, and heart failure, the aim should be to re-establish the patient on his/her normal medications as soon as is feasible in the post-operative period. This will be dictated somewhat by gastrointestinal function and any haemodynamic upset that may have occurred in the perioperative period. For abdominal surgery patients, placing a Salem sump or fine-bore feeding tube distal to the pylorus at the time of surgery will facilitate enteral drug administration even in the presence of reduced gastric emptying.

Conclusion

Dialysis-dependent ESRD is a complex and increasing healthcare problem. The frequency with which these patients present for elective or emergency surgery is appreciable. The presence of severe comorbidities and potential for clotting, fluid, electrolyte, and drug handling abnormalities in the perioperative period provides a challenge for all healthcare professionals involved in their care. Traditional approaches to recognition and management of high-risk patients are evolving as a result of research highlighting the potential for new tools to assist with preoperative diagnosis of functional compromise, optimisation of haemodynamic and tissue oxygenation, and understanding of microvascular dynamics. With careful planning, appropriate preoperative investigation, and attention to detail in the perioperative period, the probability of good patient outcomes can be maximized.

Table 1: Comorbid conditions in incident HD dialysis patients starting dialysis between 2003-2008

Co-morbidity	Number	Percentage (%)	Median age (years)
Angina	1845	16.9	71.3
MI in past 3 months	339	3.1	70.7
MI >3 months ago	1304	11.9	70.8
CABG/angioplasty	837	7.7	69.0
Cerebrovascular disease	1,177	10.8	71.1
Diabetes (not listed as PRD)	977	9.1	70.9
COPD	855	7.9	70.8
Liver disease	329	3.0	60.0
Claudication	957	8.7	70.6
Ischaemic/neuropathic ulcers	410	3.7	62.6
Angioplasty/vascular graft	411	3.8	71.4
Amputation	248	2.3	61.3
Smoking	1629	15.3	61.2
Malignancy	1457	13.3	72.0

Modified from (4)

Table 2: Components of the Revised Cardiac Risk Index (24)

Coronary artery disease
Heart failure
Cerebrovascular disease
Diabetes mellitus requiring insulin
Renal insufficiency (creatinine concentration > 176.8 μmol/L [>2 mg/dL])
High-risk non-cardiac surgery (suprainguinal vascular, intrathoracic, or intraperitoneal procedures

Each component receives 1 point if present, with scores of 2 or more representing intermediate to high risk of cardiac complications.

Table 3: Characteristics of opioids and their metabolites in renal failure and dialysis

Opioid	Metabolism	Metabolites (IA) = Inactive (A) = Active	Excretion	Accumulation In Renal Failure	Removed by HD	Safety profile in HD patient
Morphine	Hepatic	Normorphine (IA) Morphine 3-glucuronide, (IA) Morphine 6-glucuronide (A)	Renal	Yes	Yes	Reduce dose and increase interval. Extreme caution required
Fentanyl	Hepatic	Norfentanyl (IA)	Renal (7% unchanged)	Parent compound may accumulate	No	Safe – reduce dose
Alfentanil	Hepatic	Noralfentanil (IA)	Renal	No	No	Safe – reduce dose due to increased free fraction
Remifentanil	Blood & tissue esterases	GR90291 (IA)	Renal	No	No	Safe
Codeine	Hepatic with polymorphism	Codeine-6-glucuronide (A) Norcodeine (IA) Morphine (A) Normorphine (IA) Morphine 3-glucuronide, (IA) Morphine 6-glucuronide (A)	Renal	Yes	Limited data	Avoid – serious adverse effects have been reported
Oxycodone	Hepatic with polymorphism	Noroxycodone (IA) Oxymorphone (A) Conjugated oxymorphone (IA)	Renal	Yes	No data	Ideally avoid. If used, reduce dose and increase interval. Extreme caution required
Tramadol	Hepatic	O-dimethyl-tramadol (A)	Renal	Yes	Yes	Avoid – lowered seizure threshold and altered mental status
Meperidine	Hepatic	Normeperidine (A) Normeperidinic acid Meperidinic acid	Renal (5% unchanged)	Normeperidine accumulates	No (Normeper-idine)	Avoid – Metabolite accumulation causes seizures

Methadone	Hepatic		Renal and fecal	-	No	Appears safe
Hydromorph-one	Hepatic	Hydromorphone-3-glucoronide (neuro-excitation)	Renal	Yes	Yes	Neuro-excitation possible. Use lower dose or longer interval. If used, additional dose may be needed after HD

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