Gastrointestinal dysfunction following cardiac surgery

Sunil K Ohri and Theo Velissaris

Wessex Cardiothoracic Centre, Southampton General Hospital, Southampton, UK

Introduction

Organ and tissue injuries are well-recognized sequelae to cardiac surgery, but until the advent of off-pump coronary artery bypass (OPCAB) procedures, these were considered a consequence of cardiopulmonary bypass (CPB). Despite the deterioration of the risk profile of patients presenting for cardiac surgery, the overall incidence of gastrointestinal (GI) complications has changed little over the last two decades, which may be a result of improvements in cardiac surgical techniques, anaesthesia and intensive care. The lethality of GI complications has also altered little over this time frame, which underpins their clinical importance and the need to identify and intervene at the earliest stage if outcome is to be influenced.

Clinical presentations and risk factors

The most common clinical complications in descending order of frequency are GI haemorrhage, intestinal ischaemia, pancreatitis and cholecystitis. A period of ileus or constipation is probably the most common complication, but is usually clinically insignificant and, therefore, not recorded as a morbidity. Overall, the incidence ranges from 0.3 to 2.0%, with mortality ranging from 10 to 60%. In our own retrospective study, using univariate analysis, we identified seven risk factors: Inotropic support, Intra-aortic balloon pump support, Arrhythmias, Pre-existing renal dysfunction (creatinine > 125 μmol/L), Established renal failure, Pre-existing hepatic dysfunction (bilirubin > 14 μmol/L), Protracted ventilation ( > 24 h).

These all pointed to hypoperfusion of the splanchnic bed as the common factor in the peri-operative period in the pathogenesis of these complications.

Subsequently, numerous studies have identified other factors, including low ejection fraction and peripheral vascular disease, which may be important in identifying at-risk patients, but more recently, multivariate analysis has been applied to identify independent risk factors. In a study of 11 058 patients by D’Ancona et al., using stepwise logistic regression analysis, six independent risk factors were identified:

- Prolonged mechanical ventilation ( > 24 h, odds ratio 5.5)
- Postoperative renal failure (odds ratio 4.2)
- Sepsis (odds ratio 3.6)
- Valve surgery (odds ratio 3.2)
- Preoperative renal failure (odds ratio 2.7)
- Deep sternal infection (odds ratio 2.4)

This study is notable, firstly, because of the population size studied, but it also reflects modern cardiac surgical practise using a modern CPB protocol and patients with a mean Parsonnet score of 16.6 in those with GI complications and 12.1 without GI complications (p < 0.0001, univariate analysis). It is interesting that, despite the time interval, two factors appear to be consistently prominent using either univariate or multivariate analysis, and these are pre/postoperative renal impairment and protracted ventilation ( > 24 h). The link between renal dysfunction and GI complications may be explained by hypoperfusion, which affects the renal and gut beds in a similar fashion, and injury to these two beds is likely to run in parallel. Renal failure also results in impaired jejunal motility and decreases colonic transit time. Protracted ventilation has been identified as a risk factor for GI morbidity by numerous univariate analyses and was first noted in multivariate analysis by Spotnitz et al., with an odds ratio of 6.6. During mechanical
ventilation, hypoperfusion to the splanchnic bed may be induced by the use of positive end-expiratory pressure (PEEP). PEEP reduces venous return and, thereby, cardiac output and blood pressure. High PEEP levels can induce angiotensin and catecholamine production, leading to splanchnic vasoconstriction. Patients who have had a stormy operative course are, therefore, put at further risk for GI complications by the need to use prolonged mechanical ventilation, often with intra-aortic balloon pump (IABP) support, with or without renal support. All these factors have the potential to reduce the limited flow to the splanchnic bed in patients who already have a compromised cardiac output.

It is pertinent to note that valve surgery has been noted as a risk factor in both univariate and multivariate analyses. It may be argued that valve patients are more at risk of embolic injury and, indeed, in a postmortem study, the GI tract was the most frequent site for atheroembolism. Atheroembolism may also be the mechanism of injury in patients who have aorto-iliac disease and receive IABP support. Although GI haemorrhage is the most frequently reported GI complication after both coronary and valve surgery, the aetiology is probably two-fold; haemorrhage secondary to over anti-coagulation of mechanical valve patients and haemorrhage due to primary mucosal injury from hypoperfusion. The majority of patients sustain GI haemorrhage secondary to mucosal injury, since only 24% of valve patients who sustained GI bleeding had been over anti-coagulated.

The largest randomized study of 300 patients found a 7.3 versus 0.7% (CPB versus OPCAB) incidence of GI complications, with CPB identified as the only risk factor for this morbidity on multivariate analysis. The high incidence of GI complications in this relatively low-risk cohort (Parsonnet score 7.5 and median number of grafts 2) suggests that the sample size is still a limiting factor in this study. More conclusive evidence may be forthcoming from database analysis using propensity matching of OPCAB and CPB patients.

Liver dysfunction

Liver dysfunction following cardiac surgery has been less well documented, but is worthy of mention because liver failure is extremely difficult to treat and often fatal after cardiac surgery. Liver dysfunction may present as mild hyperbilirubinaemia, or much less commonly, as liver failure as part of multi-system organ failure. The incidence of hyperbilirubinaemia has been reported at 14–20% post-CPB. Collins et al. documented, in a prospective study of 248 patients undergoing CPB, that preoperative alcohol intake, hepatic enzymes and bilirubin were not associated with subsequent liver dysfunction, but raised right atrial pressure, and multiple valve replacements were significant prognostic factors, which may have importance to the rising population of adult grown-up congenital heart (GUCH) patients presenting for surgery. This contention has been supported by Chu et al. who documented a 21.7% incidence of hyperbilirubinaemia amongst patients undergoing congenital cardiac procedures. Valve patients also had a high incidence; these findings correlated well with high right-sided pressures which would cause liver congestion or valve lesions causing tricuspid incompetence. These patients have reduced hepatic reserve and do not sustain the insult of cardiac surgery and CPB as well those without pre-existing hepatic congestion. Using the galactose clearance technique, hepatic blood flow was found to be reduced by 19% during CPB. The blood supply to the liver is also dependent on the perfusion protocol adopted; Mathie et al. found hepatic perfusion was preserved during CPB by pulsatile flow at normothermia, but this advantage is less apparent at hypothermic temperatures (28–30°C). The duration of CPB (>80 min) has also been described as a risk factor for hepatic damage, as measured by reduced monoethylglycinexylidide (MEGEX) hepatic production and γ-glutathione S-transferase (γGST) release as a marker of liver injury. In a recent analysis of a prospectively collected database, the incidence of severe ischaemic early liver injury (SIELI) was 1.1% (20 of 1800 patients) with a mortality of 65%. This mortality is higher than that reported in other series of ischaemic hepatitis and was associated with low cardiac output and high right-sided filling pressures, postoperatively. Although multivariate analysis identified female gender as the only independent risk factor, the authors concluded that the main risk factors were hepatic hypoperfusion and elevated cardiac filling pressures. In our own unit, with the aim of identifying the potential benefit of eliminating CPB as a predisposing factor for liver injury, we have completed a prospective, randomized study in low-risk patients undergoing CABG. In this study, there was no difference in liver dysfunction between patients undergoing CPB using pulsatile flow at 32°C and OPCAB grafting. The markers of liver injury that were measured included MEGEX, bilirubin and liver enzymes (unpublished data). This finding, together with other data to be presented, supports...
the growing evidence that CPB alone is not responsible for tissue and organ injury.

**Alterations in splanchnic perfusion during cardiac surgery**

CPB poses significant challenges to the splanchnic and renal beds during CPB. Unlike the cerebrum, which has a profound ability to autoregulate and maintain tissue perfusion at a time of reduced blood pressure and flow, the splanchnic and renal perfusion are reduced.27

Normally, the gut receives approximately 25% of the cardiac output, but re-distribution of blood flow occurs to other tissue beds at times of shock or haemodynamic stress. Rowell and Johnson found that hypothermia in normal human volunteers reduced splanchnic blood flow.28 The mesenteric vasculature may be considered to consist of three primary parallel circuits serving the muscularis propria, serosa and mucosa. Each circuit is composed of five series-coupled components. Sequentially, they are the arterioles, pre-capillary sphincters, capillaries, post-capillary sphincters and the venous capacitance vessels. The resistance arterioles primarily govern vascular resistance and vasodilate in response to reductions in mean arterial pressure (MAP). This is both a direct myogenic response to a reduction in MAP and a metabolic response to the accumulation of local metabolites, such as adenosine.29 In addition to autoregulation of total blood flow, re-distribution of blood flow occurs within the gut wall, so, with increasing reductions in MAP blood flow, becomes prioritized to the villi at the expense of the deeper layers of the gut wall.30 This makes teleological sense, since the mucosa is the most metabolically active part of the gut wall. However, in circulatory shock, these autoregulatory mechanisms are overridden, with local and systemic vasoconstrictors acting upon resistance arterioles to reduce mesenteric perfusion.29 The state of mesenteric autoregulatory mechanisms during CPB and, in particular, the effects of hypothermia are unknown, but hypoperfusion may occur as a result of increases in arteriolar and pre-capillary sphincter tone by the action of systemic vasoconstrictors. Adrenergic stimuli act predominantly upon the post-capillary capacitance vessels to autotransfuse the individual and improve cardiac output by increasing preload of the heart.31

One of the major consequences of CPB is a progressive increase in systemic vascular resistance, particularly if non-pulsatile perfusion is used during the extracorporeal perfusion period. The loss of pulsatility in the renal arteries, together with a reduction in MAP during CPB, is associated with increased renin release. The end-product of the renin–angiotensin axis is the production of angiotensin II. The secretion of this hormone may be ameliorated by the use of angiotensin-converting enzyme inhibitors or by the employment of pulsatile perfusion.32 Angiotensin II is a highly selective mesenteric vasoconstrictor with high affinity receptors for this peptide hormone on splanchnic vascular smooth muscle, and much of the increase in the systemic vascular resistance index (SVRI) during CPB may be mediated via mesenteric vasoconstriction. Evidence for the importance of this hormone in the development of non-occlusive mesenteric ischaemia has been found in animal models of cardiogenic shock. Angiotensin II is not the only candidate that may mediate mucosal hypoperfusion during bypass.

**Inflammation and mesenteric vasomotion**

CPB results in a whole host of inflammatory mediators due to the bio-incompatibility of the extracorporeal circuit. Products of this inflammatory response have profound vasoactive properties, which may be important at the pre-capillary or tissue level. These mediators include C5a, thromboxanes (A2 and B2) and leukotrienes. All have been found to be potent mesenteric vasoconstrictors in different animal models.33,34 Complement activation with the release of C3a and C5a induces increased vascular permeability, vasoconstriction, neutrophil activation, and cytokine expression (tumour necrosis factor (TNF), interleukins IL-1, -6 and -8). TNF and IL-1 induce vasodilatation and expression of specific adhesion molecules, such as E-selectin and intercellular adhesion molecule-1 (ICAM-1), which promote adhesion of leukocytes to endothelial cells (rolling and margination) prior to ingress into tissues to cause neutrophil-mediated damage.35

The interaction of these vasoactive mediators with endothelium to modulate vascular tone has only recently been investigated. In a rat model of CPB, Douget et al. found that 90-min CPB provoked an early and transient mesenteric endothelial dysfunction with moderate impairment of endothelium-dependent relaxation. In addition, mesenteric arteries showed an increased contractile response to phenylephrine (α1-adrenergic agonist).36 However, the impairment of mesenteric endothelium-dependent relaxation was observed shortly after CPB and was transient and temporarily related to a decline in the inflammatory marker TNF. In a porcine model, Tofukudji et al.37 reported the role
of C5a on mesenteric dysfunction and found impairment of mesenteric artery relaxation in pigs in response to ADP and substance p, when comparing the sham group; endothelium-independent relaxation to sodium nitroprusside (SNP) was not altered.\(^3^7\) The effect of CPB on endothelial function depends on the vascular territories studied with endothelium-dependent vasodilatation in the pulmonary and renal arteries remaining unaffected.\(^3^8^,3^9\) In addition, Doguet et al. found an increase in contractile response in ileal arteries to phenylephrine, which was not altered after \textit{in vitro} nitric oxide (NO) synthase inhibition.\(^3^6\) This would suggest that NO production alone is not responsible for modulating vascular tone in the presence of inflammation and vasoconstrictors. The response to phenylephrine is regionalized, with O’Dwyer et al.\(^4^0\) reporting that, during CPB, phenylephrine had minimal effects on femoral vascular resistance, but greater effects on the splanchnic and renal beds. Therefore, maintaining perfusion pressure during CPB with alpha agonism may be at the expense of splanchnic perfusion.

This area of research introduces the concept of \textit{inflammatory mediated endothelial dysfunction and priming}. Apart from the recognized actions of inflammatory mediators, they are also responsible for region-specific alterations in vasomotion. It is pertinent to note that surgical trauma without CPB induces an inflammatory response, as observed in patients undergoing OPCAB surgery.\(^4^1^,4^2\) Therefore, the theoretical benefits of OPCAB surgery may be attenuated in patients at low risk of GI complications. Evidence from clinical research has demonstrated altered vasomotion and evidence for increased mesenteric resistance in patients undergoing CABG by interrogation of the superior mesenteric artery using Doppler ultrasound. In this latter study, the normal triphasic waveform became biphasic after CPB, with an increase in the resistivity and pulsatility indices, both indicating a rise in vascular resistance.\(^4^3\)

**Mucosal oxygenation**

Whatever the underlying mechanisms involved in the regulation of mucosal perfusion, the ultimate aim is the maintenance of adequate supplies of nutrients, particularly oxygen, to the mucosal cells. Gut tissue oxygenation \((pO_2)\) is dependent upon the balance between oxygen delivery \((DO_2)\) and consumption \((VO_2)\). The \(DO_2\) is dependent upon haemoglobin concentration, the percentage of haemoglobin saturated with oxygen in arterial blood, the affinity of haemoglobin for oxygen, cardiac output and the distribution of perfusion. During steady state conditions, \(VO_2\) is independent of \(DO_2\). Only when delivery is compromised by hypoxia/ischaemia does \(VO_2\) become dependent upon \(DO_2\). In some pathological states, such as sepsis and adult respiratory distress syndrome, \(VO_2\) is supply dependent, ie, graded reductions in \(DO_2\) cause similar reductions in \(VO_2\), which may be due to an underlying defect in tissue oxygen extraction. The ability of the gut to withstand hypoxic stress is far greater than ischaemic stress. In a dog model, reducing \(DO_2\) to \(<60\%\) by hypoxia alone caused a reduction in gut \(VO_2\). When \(DO_2\) was compromised by both hypoxia and ischaemia, and decreased to only \(51\%\), a reduction in the \(VO_2\) was observed.\(^4^4\) The point at which reductions in \(DO_2\) result in decreases in \(VO_2\) is known as the critical \(DO_2\) value. The critical \(DO_2\) value is higher for gut tissue than non-gut tissue, which is reflected by the gut having lower maximal oxygen extraction fractions than other tissues.\(^4^5\)

The intestine matches \(VO_2\) with \(DO_2\) by two distinct mechanisms. The first is based on the metabolic demand theory of local vasoregulation. Microvascular smooth muscle tone (pre-capillary sphincters) responds to local tissue metabolites, in particular, a low \(pO_2\), and vasodilate to increase the number of perfused capillaries. This latter mechanism is independent of nervous and humoral influences. This is the main mechanism that operates with moderate reductions in \(DO_2\). The increase in perfused gut capillaries enables a greater fraction of the supplied oxygen to be extracted. Only with greater reductions in the \(DO_2\) does arteriolar vasodilation also occur to increase blood flow.

The inadequacy of tissue oxygen causes a reduction in energy stores, as mitochondrial oxidative phosphorylation can no longer continue and the cell shifts to anaerobic glycolysis in an attempt to maintain cellular ATP levels. Continued glycolysis in the face of reduced \(DO_2\) results in the accumulation of lactic acid and hydrogen ions. Intracellular acidosis, as determined by tonometry, may, therefore, be a good indicator of tissue oxygenation. Poole et al. found, in a canine model, that graded reductions in intestinal blood flow resulted in linear reductions in the gut intramucosal pH (pHi).\(^4^6\) In our own clinical study, gastric pHi declined slightly during the initial phase of hypothermic CPB, but there was a progressive trend towards mucosal acidosis or hypoxia in the post-CPB period.\(^4^7\) Both CPB and the post-CPB periods are notable for reductions in \(DO_2\) secondary to reductions in haematocrit and/or cardiac index. For hypothermic...
CPB, this may not be entirely offset by a decrease in the metabolic rate with core cooling. The deterioration in the pH occurs despite increases in gastric laser Doppler blood flow. If this suggests that, during this period, there is a disparity between VO₂ and DO₂, with net ATP hydrolysis and the accumulation of H⁺ ions. Several explanations may account for this fall in gastric pH. Firstly, with a return of mucosal blood flow towards pre-CPB levels, tissue [HCO₃⁻] will approximate more closely to arterial [HCO₃⁻], thus, reducing the pH. Secondly, rewarming/reperfusion results in an increase in the metabolic rate, but, during this period, the oxygen-carrying ability of the blood remains limited, since haematocrit is reduced (mucosal haematocrit may even be less at only 50% of the systemic value) and the cardiac index is often below the physiological level of 3.0–3.2 L/min/m². This assumes that rewarming returns tissue metabolism to pre-CPB levels for any given temperature, which may be untrue. The generalized inflammatory response, with damage to cellular membranes, may increase the metabolic demand of cells. Energy requirements of the gut epithelium, damaged by CPB and/or surgery, may be increased from membrane pumps to preserve intracellular homeostasis. Under these circumstances, normal levels of DO₂ may be inadequate to prevent net degradation of ATP. Endotoxaemia during CPB may be contributory to this phenomenon. Endotoxaemia during CPB increases soon after crossclamp release, coinciding with a reduction in pH, and endotoxin is known to increase the rate of metabolism and can uncouple mitochondrial phosphorylation. Further evidence for the presence of anaerobic metabolism has been found in a skeletal muscle biopsy study of patients. This latter study, in which skeletal muscle biopsies were obtained after hypothermic bypass, found a persisting oxygen deficit in the tissues, exhaustion of the cell’s functional reserve and an activation of anaerobic metabolism.

A canine model of CPB has found that mucosal acidosis coincides with increased gut VO₂ at a time when DO₂ was relatively fixed. This decline in the pH coincided with reduced pO₂ in the mesenteric vein. Mucosal oxygenation is further reduced by the counter-current exchange of oxygen, which progressively reduces villus pO₂ from the base to the tip. Thus, mixed systemic or mesenteric venous sampling does not indicate actual villus tip oxygenation because of the counter-current exchanger and of villus arterio-venous oxygen shunting. The magnitude of the insult has been related to the duration of CPB, with patients demonstrating more severe mucosal acidosis and evidence of liver injury when the CPB time exceeded 80 min. These findings may have implications for the normal physiological functions of the gut in the postoperative period, in particular, its function as a barrier to luminal toxins.

In a randomized study of low risk patients undergoing OPCAB surgery, we found very similar trends in mucosal hypoxia post-surgery compared to CABG with CPB. We hypothesize that this may be due to the on-going activation of the inflammation, albeit attenuated by avoiding contact activation, but, in addition, OPCAB patients sustain repeated periods of hypotension and impaired cardiac index which result from manoeuvres required to position the myocardium for revascularization (Figure 1). The study findings suggest that, although the use of CPB may contribute to the development of gut mucosal hypoxia, factors such as perioperative haemodynamic stability and the use of vasoconstrictors are of paramount importance. In the same study, we also observed a significant association between pH and global oxygen extraction fraction, with worsening gastric mucosal oxygenation during increased global oxygen extraction. This finding is similar to the previously reported association between pH and SVo₂ and indicates that the gut becomes particularly susceptible to injury at times of increased global oxygen demand. The release of endogenous catecholamines and other stress hormones in the perioperative period may also play a pivotal role in the increase in global Vo₂ and the disturbance in gut oxygen supply and demand ratio. In a randomized study of low risk patients undergoing coronary surgery with CPB versus OPCAB, we observed a similar pattern of transient increase in cortisol and vasopressin levels with no significant differences between the two groups. The comparable release of stress hormones after surgery with CPB versus OPCAB may provide a further explanation of why the avoidance of CPB does not appear to confer a significant advantage in gut mucosal oxygenation.

**Gut function and OPCAB**

The gut has absorptive and barrier functions, which are vital for the survival of the patient. These functions have been investigated clinically using saccharide probes. The main findings are that absorptive capacity is reduced after surgery and barrier function is impaired, as measured by increased permeability ratio. This may explain the endotoxaemia which is described for CPB patients. It is interesting to note that a very similar
rise in gut permeability was found for patients who underwent CABG with CPB or OPCAB surgery, but the OPCAB patients recovered faster than the CPB patients (Figure 2). These findings may be explained by both groups sustaining an inflammatory response and haemodynamic stress albeit of varying degrees and different origins.

Our findings of comparable gut mucosal hypoxia, hepatic injury and decline in intestinal function in the immediate postoperative period between OPCAB and CPB are immediately relevant to the clinical findings of two recent retrospective studies that demonstrated a similar incidence of GI complications after cardiac surgery with and without CPB. Musleh et al. reported their findings on 2327 patients undergoing surgery with CPB (1210 cases) or off-pump (1117 cases) over a 4-year period. They observed GI complications in 14 patients (1.2%) in the on-pump group, versus 18 patients (1.6%) in the off-pump group, with a resultant mortality of 28.6 versus 22.2%, respec-
tively. Their analysis demonstrated that renal dysfunction, older age and previous GI surgery were the only factors associated with a higher risk of GI complications. Similar results were obtained by Sanisoglu et al. in their retrospective study involving 1146 patients. The authors concluded that older age and extracardiac atherosclerosis were the main predictors of adverse GI outcome. They also observed that prolonged CPB (over 98 min) was associated with a higher incidence of GI complications. Our results are in keeping with the results of these retrospective studies and provide a possible explanation for these findings. Interestingly, in a randomized study of 300 patients, there was a 7.3 versus 0.7% (CPB versus OPCAB) incidence of GI complications, with CPB identified as the only risk factor for this morbidity on multivariate analysis. The unusually high incidence of GI complications in this relatively low-risk cohort (Parsonnet score 7.5 and median number of grafts 2) would suggest that the sample size may have been a limiting factor in this study. More conclusive evidence may be forthcoming from further database analysis using propensity matching of OPCAB and CPB patients.

**Summary**

- Cardiac surgery is associated with a low incidence of GI complications, but with a disproportionate mortality.
- A number of risk factors have become established which identify patients at risk.
- CPB is associated with profound reductions in mucosal blood flow.
- Mesenteric perfusion is altered by primary endothelial dysfunction, which may further be exacerbated by the use of vasoconstrictors during CPB; inflammatory mediators can ‘prime’ the mesenteric vasculature.
- Cardiac surgery with or without CPB is associated with increased tissue oxygen demands, particularly by the splanchnic bed.
- The disparity in general and regional oxygen supply and demand results in the development of mucosal hypoxia and this cannot be attributed to CPB alone.
- This injury is measurable by reductions in both absorptive and barrier functions of the gut.
- Protection may be conferred by modulating the perfusion protocol during bypass and pharmacological interventions which modify the inflammatory response to surgery.

**References**

Gastrointestinal dysfunction following cardiac surgery
SK Ohri and T Velissaris


52 Del Canale S, Vezzani A, Belli I et al. Comparative clinical study on the effects of cardiopulmonary bypass with different flows and pressures on skeletal muscle cell metabolism in patients undergoing...


Copyright of Perfusion is the property of Arnold Publishers and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.