REVIEW ARTICLE
Paul G. Barash, MD
Giovanni Landoni, MD
Section Editors

The Role of Nonocclusive Sources of Acute Gut Injury in Cardiac Surgery

Jörn Karhausen, MD, and Mark Stafford-Smith, MD, CM, FRCPC

MORE THAN HALF of all major gastrointestinal complications after cardiac surgery involve the bowel (Table 1).[1] While relatively uncommon (0.3%-6.1%),[2–14] serious conditions involving mesenteric ischemia generally are associated with difficult postoperative courses and high mortality risk (18%-58%).[1,6,12] Notably, recent studies provided plausible evidence that modest unappreciated nonocclusive acute gut injuries (AGI) also may be important (and more common) as contributors to adverse outcome after cardiac surgery. Here, mucosal hypoperfusion has been proposed as a unifying pathophysiologic mechanism for a wide spectrum of AGI, which extends from subtle functional abnormalities to extensive necrosis of the gut wall.[5,6,8,10,14,22–25]

The bowel harbors trillions of bacteria, an arsenal of activating factors separated by a single epithelial cell layer from the body's largest immune defense system within the intestinal wall. Modest loss of intestinal barrier integrity due to subclinical AGI may be sufficient to trigger or contribute to systemic inflammatory effects such as organ failure (myocardial,[15,16] respiratory,[17] renal,[18] and neurologic[19] dysfunction, and bleeding disorders).[18,20] Given the ever-worsening risk factor profile of patients presenting for cardiac surgery and the increasing complexity of procedures, the incidence of AGI is likely to increase. This review focuses on existing evidence that distinguishes vascular nonocclusive from occlusive sources of AGI, including advances in understanding of bowel microcirculatory vulnerability and parallels and potential for "crosstalk" between AGI and acute kidney injury (AKI) during cardiac surgery.

CLINICAL PRESENTATIONS OF AGI RELATED TO CARDIAC SURGERY

The spectrum of perioperative bowel complications collectively referred to as AGI is discussed (Table 1).

Gastrointestinal Bleeding

Significant gastrointestinal (GI) bleeding is the most commonly diagnosed AGI, complicating approximately 39% of all cardiac surgery procedures.[1] In their review, Rodriguez and colleagues found that among the identified bleeding sources, more are located in the upper- than in the lower-GI tract by a ratio of 3:1, but noted that approximately one third of reported GI bleeds include no identified location. Mortality rates for upper, lower, and unreported GI bleeding sources were 19, 17.4, and 38%, respectively, with patients requiring operative intervention collectively having a 49% mortality rate. Gastric and duodenal locations are the most common upper GI bleeding sites. Lower GI bleeding is most often from diverticula (40%) or vascular malformations (30%); also contributing are colitis (10%-15%), neoplasia (5%-10%), and anorectal bleeding (5%-10%).[21] It is also noteworthy that gastrointestinal arteriovenous malformations and associated episodes of bleeding are more prevalent in patients with aortic stenosis[22] and left ventricular assist devices[23] due to the reduction of von Willebrand's factor (vWF) multimers (Heyde Syndrome).

The majority of bleeding complications are thought to be the consequence of ischemic intestinal wall injury with subsequent vascular erosion.[1,24] Risk factors include prolonged cardiopulmonary bypass (CPB), aortic cross-clamp duration, extended need for positive-pressure ventilation, and advanced patient age.[24,25] In-hospital medications in one study of 131 post-cardiac surgery patients undergoing endoscopy for upper GI bleed (nonvariceal) included a variety of antiplatelet (aspirin 88.5%, clopidogrel 22.9%, nonsteroidal anti-inflammatory agents 42%) and anticoagulant agents (heparin 95.4%, low-molecular-weight heparin 6.9%, warfarin 48.1%).[26] In contrast, serious upper GI bleeding attributed to intraoperative transesophageal echocardiography (TEE) is rare ($<1\%$),[27] although at least 13 major bleeds have been reported.[28] It is noteworthy that, while Hilberath and colleagues in their safety review recommended TEE probe placement before heparin anticoagulation, they also noted similar upper GI bleed rates with or without intraoperative TEE.[28] Indeed, even the relative safety of TEE in the presence of cirrhotic gastroesophageal varices has been highlighted.[29]

Perforated Ulcer

Perforated gastric or duodenal ulcer constitutes approximately 6% of all GI complications, with a 36% mortality rate.[1] Since Mead and Folk's retrospective study published in 1969,[30] peptic ulcer prophylaxis has become routine practice. The primary approach to therapy involves operative treatment.

From the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

Address reprint requests to Jörn Karhausen, MD, Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710. Tel: +919 681 0862; Fax: +919 681 8994, E-mail: jorn.karhausen@dm.duke.edu

1053-0770/2605-0031$36.00/0
http://dx.doi.org/10.1053/j.jvca.2013.04.016
Key Words: intestinal injury, cardiac surgery, multiorgan failure, acute kidney injury, systemic inflammatory response syndrome

Table 1. Incidence and Mortality of Gastrointestinal Complications[1]

	Incidence	Fraction of all GI complications	Mortality (%)
GI Bleed	0.39%	33%	18%
Peptic Ulcer Disease	0.07%	6%	36%
Mesenteric Ischemia	0.16%	13.1%	50%
Liver Failure	0.03%	2.2%	56%
Pancreatitis	0.13%	12.8%	20%
Cholecystitis	0.11%	9.3%	27%
Diverticulitis	0.03%	2.6%	21%
Other		21%	—

Abbreviation: GI, gastrointestinal.

Mesenteric Ischemia

Normally, 20% of cardiac output (35% postprandially) enters the visceral circulation, with three quarters of total mesenteric blood flow directed toward the (metabolically active) villi and mucosal gut lining. In healthy people, splanchnic autoregulation (metabolic and myogenic relaxation) maintains perfusion through a wide range of blood pressures.[33] However, below 70 mmHg, mesenteric perfusion has a linear relationship with pressure, and increased oxygen extraction compensates to maintain tissue viability. Below 40 mmHg, oxygen extraction reserve is exhausted and the gut becomes ischemic. Under experimental conditions, total gut ischemia causes structural damage to villi within 15 minutes.[34] Understanding of the effects of CPB and extreme hemodilution on gut perfusion are limited but will be outlined in a subsequent section.

Major mesenteric ischemic events complicate 0.16%-0.35% of all cardiac surgery procedures, with an associated 50% mortality rate.[1,10] Mesenteric ischemia can be due to a variety of causes, most commonly grouped as vascular occlusive (ie, arterial thrombosis, arterial embolus, and venous thrombosis) or nonocclusive (Fig 1). Occurrence rates for the various causes of mesenteric ischemia have been reported in general medical and surgical cohorts, with a preponderance of occlusive versus nonocclusive causes being typical.[31] For cardiac surgery patients, several authors have observed that this occlusive/nonocclusive ratio may be inverted (ie, preponderant nonocclusive); however, evidence to support this is limited to 2 studies involving small cohorts.[1,32]

Occlusive sources of mesenteric ischemia (OMI) include arterial thrombosis, arterial embolus, and venous thrombosis (Fig 1).[31] In medical and general surgical cohorts, arterial thrombosis generally is associated with a history of symptomatic atherosclerotic disease (ie, intestinal angina) preceding the event (up to 65% patients). In contrast, mesenteric artery embolus most often is accompanied by a history of left ventricular mural thrombus or left atrial appendage thrombus in the setting of atrial fibrillation. Less common causes include septic emboli from endocarditis and emboli related to cardiac tumors. Up to one third of patients also will have a history of previous embolic events, and 20% have evidence of other concomitant peripheral emboli. Mesenteric venous thrombosis most often is associated with hypercoagulable states (eg, protein C, protein S or antithrombin III deficiency, factor V Leiden mutation, anticardiolipin antibodies, malignancy, estrogens/pregnancy) or portal hypertension, but can occur spontaneously in the postcardiac surgery patient. Up to 60% of such patients have a previous history of deep venous thrombosis. Further causes of mesenteric vascular occlusion not discussed in detail here are IABP malpositioning and aortic or mesenteric dissection.

Nonocclusive mesenteric ischemic (NOMI) episodes generally are associated with cumulative vasoconstrictor effects from sources such as augmented sympathetic tone, exogenous and endogenous alpha-adrenergic agonists, vasopressin, renin,

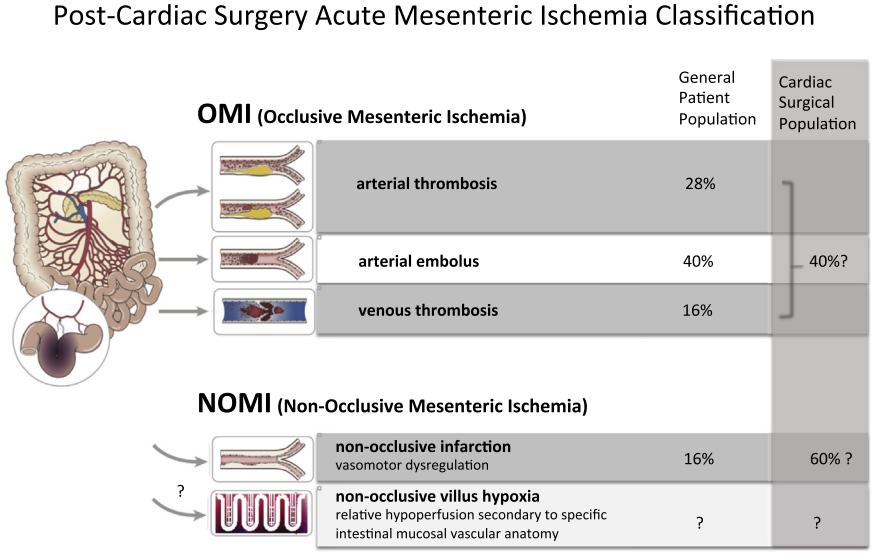

Fig 1. Classification of intestinal ischemia after cardiac surgery. Occlusive mesenteric ischemia (OMI) is distinguished from nonocclusive mesenteric ischemia (NOMI). While the respective incidence in the general surgical population is well supported,[31] the incidence in the cardiac surgical population remains poorly investigated. Of note, it is unclear based on current evidence whether or not subclinical microcirculatory nonocclusive gut injury arising from mucosal hypoxia represents a variant on a continuum with clinically obvious NOMI. Modified with permission.[35] (Color version of figure is available online.)