The Expanding Universe of Perioperative Myocardial Infarction*

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In this issue of the Journal, Parashar et al. (1) present a single-center 10-year retrospective analysis characterizing patients undergoing coronary angiography after perioperative myocardial infarction (MI). The authors present an analysis of angiograms from 1,093 patients with perioperative MI and describe the high risk nature of associated percutaneous coronary intervention (PCI). The death rate for ST-elevation myocardial infarction (STEMI) PCI patients after noncardiac surgery is alarming: the 30-day mortality rate (31.2%) is so high that these results should enhance discussions of adequate risk adjustment in national registries. Based on these important findings from the Cleveland Clinic, we can unfortunately join 3 groups together in terms of PCI risk: those with cardiogenic shock, cardiac arrest, and perioperative MI after noncardiac surgery.

This focus is important but may be too narrow. The bigger picture presented by recent studies in the area of perioperative MI is confusing: varied definitions, significant mortality, and limited preventive strategies are issues of concern (2–5). Results of this current registry extend those of prior findings: perioperative MI is not primarily a disease prevented or treated by interventional cardiologists. For example, the type of drug-eluting stent and timing of noncardiac surgery after stent placement is a focus for guidelines and research (4,6,7). However, in the current study, stent thrombosis as a cause of perioperative MI is vanishingly rare (0.7% of all patients referred for coronary angiography) (Figure 1) (1). Thus, the enhanced risk of PCI in the perioperative MI population and the factors that enhance risk should be examined in the context of an ever expanding universe of perioperative MI and injury.

**ANGIOGRAPHY AND PCI FOR PERIOPERATIVE MI**

In the current study, only 1 in 4 patients referred to the cardiac catheterization laboratory underwent coronary intervention. A detailed angiographic analysis provides insight into this restrictive use of PCI: most patients had non-flow-limiting stenoses. A simple interpretation of these observations is that perioperative MI cases are type II, an imbalance between supply and demand leading to coronary ischemia and infarction in the setting of stressful surgery (8).

There is a paucity of data regarding the mechanism of perioperative MI, few autopsy (n = 67) (9) and (n = 60) angiographic (n = 60) studies (10) from 2 decades ago provide limited conclusions. In the coronary histopathology study, perioperative MI patients demonstrated pathology similar to that of spontaneous infarctions (9). A previous Cleveland Clinic angiographic study suggested a role for chronic coronary occlusions and inadequate collateral supply in perioperative MI (10). Another relatively small angiographic registry study (n = 120) suggested that plaque rupture and type I MI characterize nearly one-half of patients with perioperative events (11). The current registry adds far more information to our understanding; this is the largest angiographic analysis of patients undergoing cardiac catheterization after perioperative MI.

What alternative interpretations of the current findings should be considered? First, maybe more patients had acute culprit lesions that could not be appreciated angiographically. The ischemic risk of angiographic moderate stenoses could have been underestimated without hemodynamic tools (12), and observation of acute thrombus formation would be diminished without intracoronary imaging.

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Furthermore, nearly 1 in 3 patients undergoing PCI for perioperative STEMI were dead at 30 days; this compares to an approximate mortality rate of 5% in previous large registry studies of spontaneous STEMI leading to primary PCI (16,17). A high PCI mortality rate has been reported for PCI among in-hospital STEMI patients who are hospitalized with other noncardiac causes (18), but the mortality rates seen in the current study highlight a cardiogenic shock level risk of PCI specifically in the perioperative setting (19). The authors identify multiple nonmodifiable risk factors for mortality that are consistent with risk factors for generic PCI, for example, baseline renal insufficiency and peripheral vascular disease. Although these risk factors may be enhanced in the perioperative population, they may not fully explain the enhanced death rates for perioperative compared to spontaneous AMI PCI.

One modifiable risk factor for post-PCI mortality was identified: bleeding. This finding is congruent with those of other studies demonstrating the risk of bleeding after PCI (20). A reduction in post-PCI bleeding risk during the time period of the study is plausible, as such trends have been demonstrated in other PCI registries (21). Opportunities for bleeding prevention are present in the current registry; for example, 1 in 4 patients received glycoprotein inhibitors for their PCI in the post-operative state, and the bleeding risk of this practice could be especially significant in the post-operative state. In addition, the use of the radial artery approach is not described but is likely <10% of the analyzed population given national trends at the time of the study (22). Of note, the interplay between surgery-related bleeding and post-PCI access-site bleeding is difficult to discern from the current registry design; the extent to which surgical and nonaccess site bleeding is modifiable in this population remains to be determined.

**BROAD CONTEXT OF PERIOPERATIVE MI**

As shown in Figure 1, the Cleveland Clinic Registry represents successive inner rings of a universe of perioperative MI, where the outer boundary is unknown, and the PCI population is small. Although stent thrombosis may remain the center of that universe, it is clearly the smallest planet in the system of perioperative MI. According to current guideline recommendations, patients undergoing noncardiac surgery do not necessarily receive post-operative troponin testing (3,4). The POISE (Perioperative Ischemic Evaluation) investigators demonstrated the potential size of the outer ring of the perioperative MI
Expanding Universe of Perioperative MI

universe, using the third universal definition of MI, 65% of post-operative MIs are without clinical symp-
toms (2); furthermore, the prognosis of a clinically silent post-operative MI is the same as that for an MI associated with symptoms, both confer an approxi-
mately 4-fold increased risk of 30-day death (2).

Thus, the 1,093 patients identified with perioperative MI represent a small to medium sized middle ring in the universe of perioperative MI; these pa-
tients are characterized by referral for coronary angiography and post-operative cardiac biomarker response >5 times the upper limit of normal. The biomarker criteria used in this study is more stringent than the third universal definition of MI (which does not require a 5-fold elevation of a biomarker) (8), thus underestimating the true denominator of this syndrome.

In addition, this denominator reflects significant selection bias. We have no reason to believe that all patients with perioperative MI are candidates for coronary angiography.

Difficulties in defining the outer ring of the perioperative MI universe are not unique to the Cleveland Clinic Registry. The appropriate diagnostic criteria defining perioperative MI is a subject of ongoing controversy. A newer term, myocardial injury after noncardiac surgery (MINS), has been proposed to more broadly describe elevated troponins after noncardiac surgery; only 1 in 6 patients with MINS has any clinical symptoms of MI (23). MINS is an independent predictor of 1-year mortality, but insights into pathophysiology and treatment options are lacking. The MANAGE (Management of Myocardial Injury after Noncardiac Surgery; NCT01661101) trial is currently randomizing patients to dabigatran, omeprazole, or placebo therapy in the continuing search for a routine prophylactic strategy to prevent myocardial damage associated with noncardiac surgery (24). Whether that trial provides new insight into therapeutic options or adds new layers to the grave-
yard of proposed prophylactic strategies (colchicine, aspirin, beta blockers, routine angiography) (3,4,15) for perioperative MI remains to be seen.

This large retrospective registry returns us to the classic angiographic studies which helped define the causes of spontaneous MI (25,26). For the first time, we have a large angiographic database on the correlates of perioperative MI. The high risk of PCI for perioperative MI is not easily explained by anatomic findings or baseline risk factors, thus, differential outcomes between PCI for perioperative and spontaneous MI may portend different underlying pathophysiology. Although the search for prophylactic and postoperative treatment strategies for perioperative MI is valuable, the current study suggests we may be launching rockets into a universe that remains largely undefined. Given the current findings of predominantly non-flow-limiting coronary stenoses, emphasis needs to be placed on using the contemporary tools of our research arsenal (i.e., cardiac magnetic resonance and optical coherence tomogra-
phy) to further understand the causes and characteristics that truly outline the broader universe of perioperative MI.

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