Etiology of Acute Coronary Syndrome after Noncardiac Surgery

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CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: The objective of this investigation was to determine the etiology of perioperative acute coronary syndrome with a particular emphasis on thrombosis *versus* demand ischemia.

Methods: In this retrospective cohort study, adult patients were identified who underwent coronary angiography for acute coronary syndrome within 30 days of noncardiac surgery at a major tertiary hospital between January 2008 and July 2015. Angiograms were independently reviewed by two interventional cardiologists who were blinded to clinical data and outcomes. Acute coronary syndrome was classified as ST–elevation myocardial infarction, non–ST–elevation myocardial infarction, or unstable angina; myocardial infarctions were adjudicated as type 1 (plaque rupture), type 2 (demand ischemia), or type 4b (stent thrombosis).

Results: Among 215,077 patients screened, 146 patients were identified who developed acute coronary syndrome: 117 were classified as non–ST–elevation myocardial infarction (80.1%); 21 (14.4%) were classified as ST–elevation myocardial infarction, and 8 (5.5%) were classified as unstable angina. After coronary angiography, most events were adjudicated as demand ischemia (type 2 myocardial infarction, n = 106, 72.6%) compared to acute coronary thrombosis (type 1 myocardial infarction, n = 37, 25.3%) and stent thrombosis (type 4B, n = 3, 2.1%). Absent or only mild, nonobstructive coronary artery disease was found in 39 patients (26.7%). In 14 patients (9.6%), acute coronary syndrome was likely due to stress-induced cardiomyopathy. Aggregate 30-day and 1-yr mortality rates were 7 and 14%, respectively.

Conclusions: The dominant mechanism of perioperative acute coronary syndrome in our cohort was demand ischemia. A subset of patients had no evidence of obstructive coronary artery disease, but findings were consistent with stress-induced cardiomyopathy. **(Anesthesiology 2018; 128:1084-91)**

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MYOCARDIAL infarction (MI) is a common and serious complication after noncardiac surgery.[1–3] Perioperative MI is associated with significant mortality that often exceeds mortality after acute MI in a nonsurgical setting.[4–6] Acute myocardial infarction often presents as acute coronary syndrome, a syndrome that encompasses several distinct entities, namely MI and unstable angina, but with similar clinical signs and symptoms (*e.g.*, chest pain). The etiology of acute coronary syndrome in a nonsurgical setting is generally well understood and involves either a thrombotic cause (plaque rupture, type 1 MI, or stent thrombosis, type 4B) or demand ischemia (type 2 MI) or a combination of the two factors.[7,8] In contrast, etiology and pathophysiology of acute coronary syndrome in the context of noncardiac surgery are incompletely understood, and there is ongoing controversy regarding whether thrombosis or demand ischemia is the dominant cause.[9–13]

The objective of this investigation was to determine the etiology of perioperative acute coronary syndrome with a particular emphasis on thrombosis *versus* demand ischemia. We studied a cohort of surgical patients who underwent diagnostic coronary angiography after presenting with acute coronary syndrome within 30 days after noncardiac surgery.

What We Already Know about This Topic

- Myocardial infarction is a common and serious complication after noncardiac surgery.
- This study determined the etiology of perioperative acute coronary syndrome with a particular emphasis on thrombosis *versus* demand ischemia.

What This Article Tells Us That Is New

- The dominant mechanism of perioperative acute coronary syndrome in this cohort was demand ischemia. A subset of patients had no evidence of obstructive coronary artery disease, but findings were consistent with stress-induced cardiomyopathy.

Materials and Methods

Study Design and Population

This was a retrospective cohort study of adult patients undergoing noncardiac surgery between January 2008 and

Corresponding article on page 1055. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). M.A.H. and A.A. contributed equally to this article.

Submitted for publication August 3, 2017. Accepted for publication January 5, 2018. From the Division of Clinical and Translational Research, Department of Anesthesiology (M.A.H., S.R., S.O., E.S., J.C.B., P.N.) and the Division of Cardiology, Department of Internal Medicine (A.A., P.L.), Washington University School of Medicine, St. Louis, Missouri.

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<zdoi;10.1097/ALN.0000000000002107>

July 2015 at Barnes–Jewish Hospital (St. Louis, Missouri) who developed acute coronary syndrome and received a coronary angiogram within 30 days of surgery. We screened the Barnes–Jewish Hospital billing database for patient records meeting inclusion criteria, reviewed the tentative list of patients case by case for potential exclusion criteria, and then matched the 146 identified patients with the local CathPCI Registry of the National Cardiovascular Data Registry, which captures all patients who undergo diagnostic angiography and percutaneous coronary intervention at our institution.[14] The study was approved by the Washington University School of Medicine Institutional Review Board (St. Louis, Missouri) and granted a waiver of informed consent, and it was not registered at a registry.

Inclusion criteria were age more than 18 yr; noncardiac surgery requiring monitored anesthesia care, general, or regional anesthesia; and the diagnosis of acute coronary syndrome. Exclusion criteria were cardiac surgery or related procedures (such as pacemaker insertion), surgery under local anesthesia, age less than 18 yr, and indications for cardiac catheterization other than acute coronary syndrome.

Measurements and Angiographic Assessment

Records were reviewed for all subjects who underwent a coronary angiogram within 30 days of noncardiac surgery and used to identify demographics, medical history, symptoms, electrocardiographic changes, cardiac biomarkers concentrations, echocardiography findings, medications, and transfusion requirements. Noncardiac surgeries were categorized as vascular *versus* nonvascular surgery. Acute coronary syndrome events were categorized as ST–elevation MI, non–ST–elevation MI, or unstable angina. The 30-day mortality and 1-yr mortality were obtained reviewing the social security registry and from the https://www.familysearch.org website (accessed July 1, 2017).

Coronary angiograms were independently reviewed by two blinded interventional cardiologists (P.L. and A.A.). In cases of discordant angiogram interpretation, angiogram findings were jointly reviewed by the interventionalists and a consensus was reached. Myocardial infarction was classified by type according to the Third Universal Definition.[15] All lesions resulting in more than 50% stenosis were analyzed and characterized by angiographic features of complexity adapted from Goldstein *et al.*[16] A lesion was considered complex if it exhibited any of the following features: (1) an intraluminal filling defect suggestive of thrombus as defined by abrupt vessel occlusion with contrast persistence; (2) plaque ulceration defined by the extension of contrast beyond but contiguous to the vessel lumen; or (3) two or more of the following: fissuring, evidenced by intraplaque dye penetration not fulfilling the definition of ulceration; irregular margins or overhanging edges; or hazy appearance. A spontaneous MI (type 1) was considered to have occurred by the presence of at least one complex lesion.

Outcomes

Primary study outcomes included types of MI: type 1 (plaque rupture, coronary occlusion), type 2 MI (demand ischemia), and type 4B (stent thrombosis); acute coronary syndrome was also classified per electrocardiogram and biomarker presentation as ST–elevation MI, non–ST–elevation MI, or unstable angina. Secondary outcomes included hospital length of stay, as well as 30-day and 1-yr mortality rates. Significant bleeding was defined as more than 1 l of blood loss.

Statistical Methods

We included a statistical analysis plan in the study protocol that was submitted and approved by the institutional review board. Primary outcomes were established *a priori*, but several additional analyses were performed *post hoc* and have been identified as such in this article. The data are presented as means and SD or medians and interquartile range for non-normally distributed data. Univariate comparisons were made with a Mann–Whitney U test, chi-square test, or Fisher exact test. We calculated unadjusted odds ratios from 2 × 2 tables. Kaplan–Meier survival analyses were performed to compare survival probabilities between types of MI and MI presentation as ST–elevation MI, non–ST–elevation MI, or unstable angina. A log-rank test was used to determine statistical significance. There was no formal sample size estimation, because the goal was to capture all patients who developed acute coronary syndrome after noncardiac surgery in our institution. Analyses were performed using SPSS 23.0 (IBM, USA) or JMP 13.2 (SAS Institute, USA). All analyses were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Study Population

After screening 215,077 patients who underwent noncardiac surgery in our hospital during the study period, the final study population of patients who underwent coronary angiography due to acute coronary syndrome within 30 days after noncardiac surgery was 146 patients (0.07%; fig. 1; table 1). More than 50% of the patients had a diagnosis of coronary artery disease, and 19% had a diagnosis of heart failure. Acute coronary syndrome after emergent surgery accounted for 8.2% of cases in this cohort (n = 12). Median estimated intraoperative blood loss was modest (150 ml, interquartile range of 0 to 405 ml), although 11.0% (n = 16) experienced significant intraoperative hemorrhage.

Acute Coronary Syndrome Events

More than 80% of acute coronary syndrome events were classified as non–ST–elevation MI (n = 117); smaller fractions were classified as ST–elevation MI (n = 21, 14.4%) and unstable angina (n = 8, 5.5%, table 2). Approximately half of events presented with clinical symptoms such as chest pain or shortness of breath; 22% of events were clinically silent. Electrocardiogram changes consistent with myocardial ischemia were observed in more than 90% of patients. Eight

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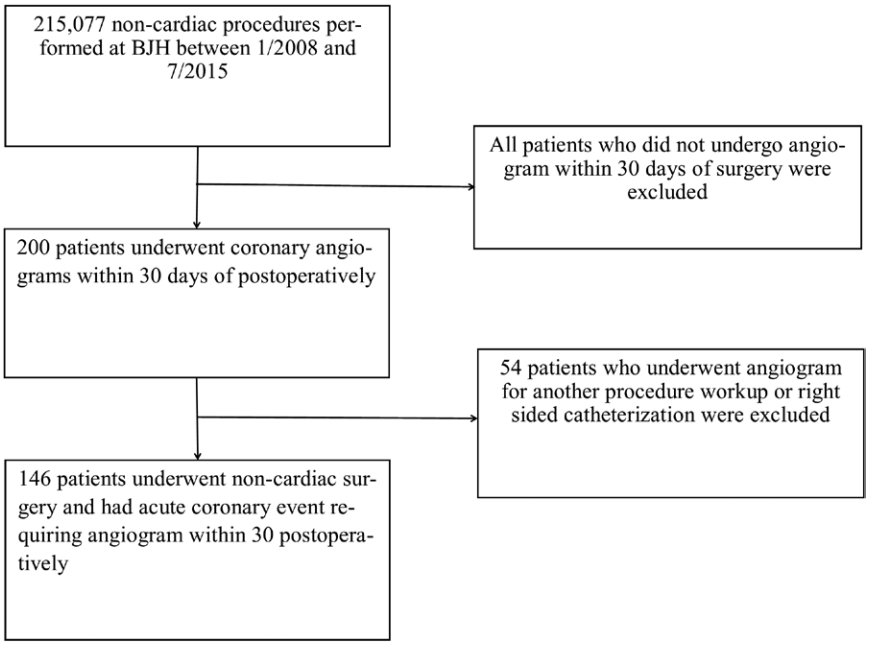

Fig. 1. Study flow diagram. The diagram shows the numbers of patients screened and the final study population. BJH = Barnes–Jewish Hospital.

percent of patients presented in cardiogenic shock (n = 11). The majority of patients developed acute coronary syndrome within the first 3 postoperative days (63%, n = 92); 16% of patients (n = 23) developed acute coronary syndrome in the intraoperative period. On average, a median of 3 days passed between acute coronary syndrome presentation and coronary angiography, except for patients with acute stent thrombosis (type 4B MI; n = 3), who were taken to the catheterization laboratory on the same day.

Patients with type 1 MI received medical management in 68% of cases (n = 25), underwent coronary artery bypass grafting surgery surgery in 30% of cases (n = 11), and received a percutaneous coronary intervention (coronary stent) in 3% of cases (n = 1). Patients with type 2 MI were predominantly managed medically (94%; n = 100).

Coronary Angiography Findings

Among all acute coronary syndrome events, 73% were adjudicated as type 2 MI (demand ischemia; n = 106,) after review of angiography films. Acute coronary thrombosis (type 1 MI) was adjudicated in 25% of patients (n = 37), and acute coronary stent thrombosis (type 4B) was adjudicated in 2% of patients (n = 3; table 3). There was no association between type 1 and type 2 MI and clinical presentation as ST–elevation MI or non–ST–elevation MI (P = 0.97). Absent or only mild (nonobstructive) coronary artery disease was found in 27% of patients (n = 39), 5% of with type 1 MI (n = 2), and 35% of patients with type 2 MI (n = 37). In 10% of events (n = 14), acute coronary syndrome was likely caused by stress-induced cardiomyopathy and not by an intracoronary event. In a *post hoc* analysis, stress-induced cardiomyopathy was observed in two patients on chronic β-blocker therapy (n = 67; 3%) compared to 12 patients who did not take β-blockers (n = 79; 15%; odds ratio, 0.17; 95% CI, 0.03 to 0.78; P = 0.02).

Short- and Long-term Outcomes

Unadjusted 30-day and 1-yr mortality rates for all patients were 7 and 14%. Survival rates were not statistically significant between type 1 MI, type 2 MI, and type 4B MI (fig. 2; P = 0.52) but were statistically significant between patients who experienced an ST–elevation MI *versus* non–ST–elevation MI (fig. 3; P = 0.02). Additional results are available as Supplemental Digital Content (http://links.lww.com/ALN/B628).

Discussion

Findings from this investigation in 146 surgical patients who developed perioperative acute coronary syndrome within 30 days after surgery and who underwent coronary angiography show that: (1) three of four events were due to demand ischemia (type 2 MI) and presented as non–ST–elevation MI, (2) more than 90% had electrocardiogram changes consistent with myocardial ischemia, (3) one in four patients had no evidence of obstructive coronary artery disease, (4) 10% of events were likely due to stress-induced cardiomyopathy, and (5) acute coronary syndrome was associated with marked short- and long-term mortality (7% 30-day mortality and 14% 1-yr mortality).

Demand Ischemia versus *Thrombosis*

The results of our study suggest that most cases of perioperative acute coronary syndrome are triggered by demand

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Table 1. Baseline Characteristics of Patients

	All Patients, n = 146 (100%)	Type 1 MI, n = 37 (25.3%)	Type 2 MI, n = 106 (72.6%)	Type 4B MI*, n = 3 (2.1%)
Demographics				
Age (median [IQR])	67 [60, 74]	70 [62, 79]	67 [60, 74]	62 [59, 63]
Male sex, n (%)	81 (55.5)	28 (75.7)	50 (47.2)	3 (100)
White race, n (%)	130 (89.0)	33 (89.2)	94 (88.7)	3 (100)
Cardiac history, n (%)				
Coronary artery disease	75 (52.4)	19 (51.4)	53 (50)	3 (100)
Previous MI	43 (29.5)	9 (24.3)	33 (31.1)	1 (33.3)
Coronary artery bypass grafting surgery	30 (20.5)	7 (18.9)	22 (20.8)	1 (33.3)
Percutaneous coronary intervention	43 (29.5)	12 (32.4)	28 (26.4)	3 (100)
Congestive heart disease	27 (18.5)	4 (10.8)	22 (20.8)	1 (33.3)
Comorbidities, n (%)				
Hypertension	126 (86.3)	35 (94.6)	88 (86.3)	3 (100)
Diabetes mellitus	51 (34.9)	10 (27.0)	40 (37.7)	1 (33.3)
Hyperlipidemia	91 (62.3)	24 (64.9)	65 (61.3)	2 (66.7)
Obesity (BMI > 30)	54 (37.8)	13 (36.1)	39 (37.5)	2 (66.7)
Smoking history	105 (71.9)	27 (73.0)	77 (72.6)	1 (33.3)
Chronic kidney disease	25 (17.1)	7 (18.9)	18 (17.0)	0
Anemia, hemoglobin < 10, n (%)	19 (13)	4 (11.4)	15 (14.7)	0
Preoperative medications, n (%)				
β-blockers	67 (45.9)	19 (51.4)	45 (42.5)	3 (100)
Statins	77 (52.7)	20 (54.1)	55 (51.9)	2 (66.7)
Antiplatelets	92 (63.0)	29 (78.4)	60 (56.6)	3 (100)
ACE inhibitor	74 (50.7)	17 (45.9)	55 (51.9)	2 (66.7)
Surgery				
Duration, h (median [IQR])	2.5 [1.3, 3.7]	3.0 [1.9, 4.3]	2.5 [1.5, 3.7]	1.7 [1.7, 1.9]
Vascular surgery, n (%)	32 (21.9)	14 (37.8)	17 (16.0)	1 (33.3)
Emergent surgery, n (%)	12 (8.2)	4 (10.8)	8 (7.5)	0
Significant bleeding, n (%)	16 (11.0)	7 (18.9)	9 (8.5)	0
Intraoperative EBL, ml (median [IQR])	150 [0, 405]	200 [20, 700]	100 [0, 400]	150 [150, 500]
General anesthesia, n (%)	135 (92.5)	35 (94.6)	97 (91.5)	3 (100)

*Median values in this column are reported as median and range, not interquartile range due to the small number of observations.
ACE = angiotensin-converting enzyme; BMI = body mass index; EBL = estimated blood loss; IQR = interquartile range; MI = myocardial infarction.

ischemia, and only a small proportion are due to an acute thrombotic event, such as coronary plaque rupture. Acute coronary syndrome events captured in our cohort probably represent one of the most severe phenotypes of perioperative cardiac events, because nearly all of them were clinically readily apparent and triggered a cardiology consultation before coronary angiography. It was *a priori* unclear whether the dominant cause was acute thrombosis or demand ischemia. Mechanistically both mechanisms seemed equally probable: surgery causes acute inflammation and a prothrombotic state, whereas hypoxemia, surgical stress, hyper- or hypotension, and anemia increase demand and reduce supply. Autopsy studies of fatal MI after noncardiac surgery report about half the cases as caused by plaque rupture and acute thrombosis.[17,18] A larger proportion of thrombotic events was also reported in two separate angiography studies of nonfatal MI after noncardiac surgery: Berger *et al.*[19] found a 63% rate (n = 48), and Gualandro *et al.*[20] found a 50% rate (n = 120). Conversely, a recent angiography study reported a 22% percutaneous coronary intervention rate due to a thrombotic event among 1,093 patients with acute coronary syndrome after noncardiac surgery.[21] Duvall *et al.*[11] found a 55% rate of type 2 MI *versus* a 26% type 1 MI rate (n = 66). In a recent study among 103 veterans with coronary artery disease and previously implanted stents who developed perioperative MI, 48% were found to have demand ischemia (stable obstructive coronary artery disease), and 46% were caused by a thrombotic event.[22] It is important to note that several independent lines of evidence strongly suggest that most events of myocardial ischemia after noncardiac surgery are silent and caused by demand ischemia, as detected by Holter electrocardiogram monitoring or postoperative cardiac troponin elevation.[23–28]

Non–ST–elevation MI versus *ST–elevation MI*

The electrocardiogram presentation of acute coronary syndromes typically falls into one of two main categories: ST–elevation MI or non–ST–elevation MI (some patients have unspecific electrocardiogram changes). Transmural myocardial ischemia caused by a type 1 MI often presents as ST–elevation MI. Demand ischemia (type 2 MI) causing subendocardial ischemia presents mostly as non–ST–elevation

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Table 2. Characteristics of Acute Coronary Syndrome Events

	All Events, n = 146 (100%)	Type 1 MI, n = 37 (25.3%)	Type 2 MI, n = 106 (72.6%)	Type 4B MI*, n = 3 (2.1%)
Type of event, n (%)				
STEMI	21 (14.4)	5 (13.5)	14 (13.2)	2 (66.7)
NSTEMI	117 (80.1)	31 (83.8)	85 (80.2)	1 (33.3)
Unstable angina	8 (5.5)	1 (2.7)	7 (6.6)	0
Presentation signs and symptoms, n (%)				
Chest pain	64 (43.8)	18 (48.6)	43 (40.6)	3 (100)
Shortness of breath	23 (15.8)	6 (16.2)	17 (16.0)	0
Hypotension	22 (15.1)	4 (10.8)	18 (17)	0
Tachycardia	19 (13)	4 (10.8)	15 (14.2)	0
Hypoxemia	14 (9.6)	1 (2.7)	13 (12.3)	0
Electrocardiogram changes	132 (90.4)	33 (89.2)	96 (90.6)	3 (100)
Time of presentation, n (%)				
Intraoperative	23 (15.8)	1 (2.7)	22 (20.8)	0
Postoperative	119 (81.5)	34 (91.1)	82 (77.4)	3 (100)
Postdischarge	4 (2.7)	2 (5.4)	2 (1.9)	0
Time intervals, days (median [IQR])				
Surgery to event	1 [0, 2]	1 [0, 2]	1 [0, 3]	1 [1, 1]
Surgery to peak cTnI	2 [1, 3]	1.5 [1, 3]	2 [1, 3]	1.0 [1, 1]
Surgery to angiogram	4 [2, 7]	4.5 [2, 7]	4 [2, 7]	1 [1, 4]
Event to angiogram	3 [1, 5]	3 [1, 5]	2 [1, 5]	1 [0, 3]
Peak cTnI, ng/ml (median [IQR])	3.2 [0.9, 8.6]	5.1 [0.9, 16.0]	2.5 [0.8, 6.9]	36.3 [18.2, 39.4]
Management, n (%)				
Medical	127 (87.0)	25 (67.6)	100 (94.3)	2 (66.7)
PCI/stent	5 (3.4)	1 (2.7)	3 (2.8)	1 (33.3)
Coronary artery bypass grafting surgery	14 (9.6)	11 (29.7)	3 (2.8)	0 (0)
Hospital LOS (median [IQR])	9 [6, 14]	10 [7, 14]	9 [6, 14]	5 [5, 6]
30-day mortality, n (%)†	10 (7.1)	2 (5.6)	8 (7.8)	0
1-yr mortality, n (%)†	20 (14.2)	5 (13.9)	15 (14.7)	0

Signs and symptoms were extracted from clinical notes and not based on specific diagnostic criteria. *Median values in this column are reported as median and range, not interquartile range due to the small number of observations. †Of 141 patients.

cTnI = cardiac troponin I; IQR = interquartile range; LOS = length of stay; MI = myocardial infarction; NSTEMI = non–ST–elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST–elevation myocardial infarction.

MI. Our data showed that there was no association between type 1 and 2 MI and presentation as ST–elevation MI *versus* non–ST–elevation MI. Only acute stent thrombosis appeared to present mostly as ST–elevation MI. Therefore, it may clinically not be feasible to speculate about the underlying etiology of a perioperative acute coronary syndrome event based on its electrocardiogram presentation.

Absent or Mild Coronary Artery Disease and Stress-induced Cardiomyopathy

A surprising finding of this investigation was that in 27% of coronary angiographies after perioperative acute coronary syndrome, neither a culprit lesion nor obstructive coronary artery disease was found, with some patients having a normal coronary anatomy. In a small angiography study, Ellis *et al.*[29] also found evidence for postoperative acute coronary syndromes occurring in the absence of obstructive coronary artery disease. In 10% of our patients, the angiographic findings were most consistent with stress-induced cardiomyopathy (Takotsubo syndrome) and not a coronary process.

Limitations

This study had several limitations. First, the study population was highly selective and does not represent the full spectrum of postoperative MI or acute coronary syndrome. On the one hand, the most severe cases of postoperative acute coronary syndromes are associated with sudden cardiac death and fatal MI—patients we did not capture. On the other hand, the majority of ischemic events in the postoperative period are silent and often missed clinically. Second, the initial identification of patients was by the hospital billing database, a method with significant limitations. Although we reviewed each case and matched it with the prospectively designed National Cardiovascular Data Registry, there is a possibility we missed patients. For example, if patients presented with acute coronary syndrome to an outside hospital that was not part of our hospital network, we would have been unable to capture the event and thus missed the patient. Third, although the sample size of 146 patients represents one of the largest thus far in the literature and has been collected from more than 215,000 noncardiac surgeries at our hospital, it is still rather small and prone to bias. In addition, we cannot exclude temporal trends

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Table 3. Coronary Angiography Findings

	All Events, n = 146 (100%)	Type 1 MI, n = 37 (25.3%)	Type 2 MI, n = 106 (72.6%)	Type 4B MI, n = 3 (2.1%)
Normal or mild disease, n (%)	39 (26.7)	2 (5.4)	37 (34.9)	0
Calcification, n (%)	78 (53.4)	25 (67.6)	53 (50)	0
Haziness, n (%)	77 (52.7)	33 (89.2)	41 (38.7)	3 (100)
Ulceration, n (%)	28 (19.2)	25 (67.6)	1 (0.9)	2 (66.7)
Thrombus, n (%)	5 (3.4)	2 (5.4)	0	3 (100)
Stress-induced cardiomyopathy, n (%)	14 (9.6)	0	14 (13.2)	0

MI = myocardial infarction.

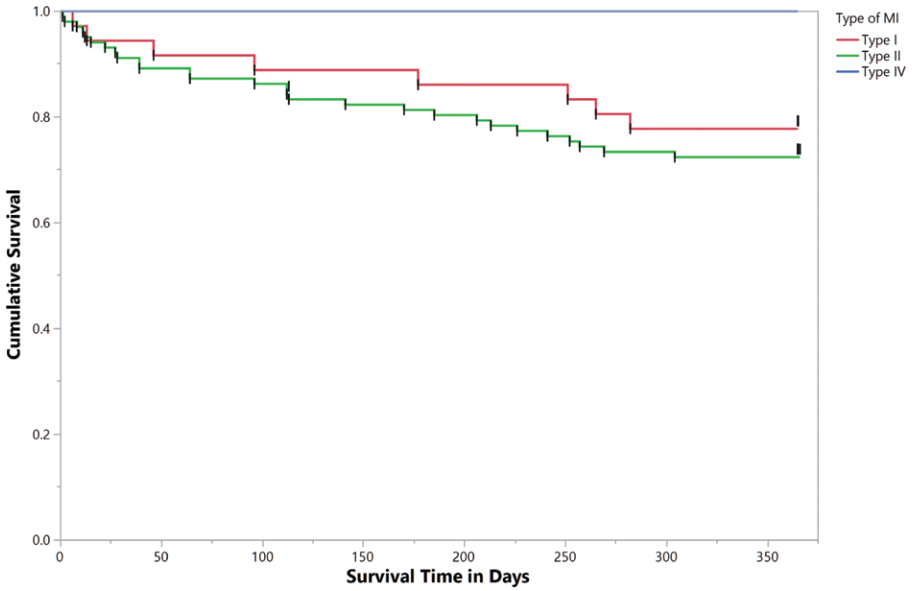

Fig. 2. One-yr mortality by type of myocardial infarction (MI). Unadjusted Kaplan–Meier survival curves compare type 1 MI (*type I*, thrombotic cause), type 2 MI (*type II*, demand ischemia), and type 4B (*type IV*, stent thrombosis). Survival probability is not statistically significant between groups (log-rank test, $P = 0.51$).

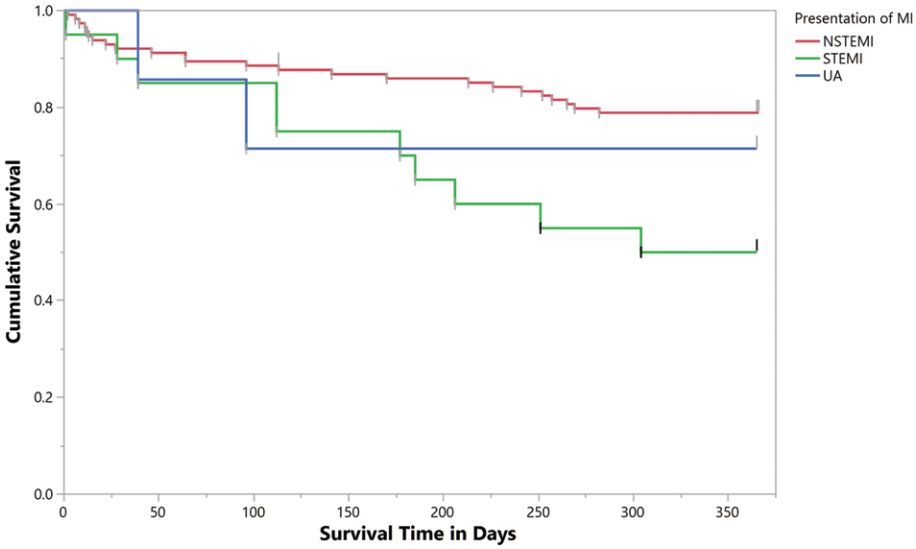

Fig. 3. One-yr mortality comparing ST–elevation myocardial infarction (MI) to non–ST–elevation MI (NSTEMI) and unstable angina (UA). Unadjusted Kaplan–Meier survival curves show a statistically significantly different survival probability between the three groups (log-rank test, $P = 0.02$).

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that may have influenced procedural and medical management of postoperative acute coronary syndrome. Lastly, we could not capture data derived from novel adjunct techniques now sometimes used during coronary angiography, such as intravascular ultrasound or data on left ventricular hypertrophy.

Conclusions and Potential Clinical Implications

Evidence from this investigation suggests that the dominant mechanism of acute coronary syndrome after noncardiac surgery is demand ischemia and that a sizable proportion of patients develop acute coronary syndrome without evidence for obstructive coronary artery disease, with some of these due to stress-induced cardiomyopathy. Thus, it appears plausible that strategies that reduce myocardial oxygen demand (*e.g.*, β-blocker therapy, adequate pain control) and increase myocardial oxygen supply (*e.g.*, adequate oxygenation and coronary blood flow, correction of anemia [if hemoglobin was less than 8 g/dl], adequate intravascular volume status, correction of hypotension) will likely have the biggest impact in preventing and treating acute coronary syndrome in patients undergoing noncardiac surgery compared to antithrombotic therapy.

Acknowledgments

The authors thank Tom C. Bailey, M.D., Division of Infectious Diseases, Washington University, St. Louis, Missouri, and John Lasala, M.D., Ph.D., Cardiovascular Division, Department of Internal Medicine, Washington University, for help with initial study design and database query.

Research Support

This work was supported by departmental funds only. Dr. Nagele is currently supported by National Institutes of Health (Bethesda, Maryland) grant No. R01HL126892. Dr. Amin is funded via a KM1 career development award from the Clinical and Translational Science Award program of the National Center for Advancing Translational Sciences of the National Institutes of Health (grant Nos. UL1TR000448, KL2TR000450, and TL1TR000449), National Cancer Institute of the National Institutes of Health (grant No. 1KM1CA156708-01), an R18 grant from the Agency for Healthcare Research and Quality (Rockville, Maryland; grant No. R18HS0224181), and two additional grants by the Barnes–Jewish Hospital Foundation (St. Louis, Missouri).

Competing Interests

Dr. Nagele reports receiving research grants and other research support from Roche Diagnostics (Indianapolis, Indiana) and research grants and other research support from Abbott Diagnostics (Lake Forest, Illinois). Dr. Amin has received research funding from Volcano (San Diego, California) and is a consultant for Terumo (Somerset, New Jersey), The Medicines Company (Parsippany, New Jersey), and AstraZeneca (Wilmington, Delaware). The other authors declare no competing interests.

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References

1. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS: Perioperative myocardial infarction. Circulation 2009; 119:2936–44
2. Adesanya AO, de Lemos JA, Greilich NB, Whitten CW: Management of perioperative myocardial infarction in noncardiac surgical patients. Chest 2006; 130:584–96
3. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S: Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. JAMA Cardiol 2017; 2:181–7
4. Ghaferi AA, Birkmeyer JD, Dimick JB: Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009; 361:1368–75
5. Browner WS, Li J, Mangano DT: In-hospital and long-term mortality in male veterans following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 1992; 268:228–32
6. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators: Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: A cohort study. Ann Intern Med 2011; 154:523–8
7. Pagidipati NJ, Peterson ED: Acute coronary syndromes in women and men. Nat Rev Cardiol 2016; 13:471–80
8. Libby P: Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013; 368:2004–13
9. Biccard BM, Rodseth RN: The pathophysiology of peri-operative myocardial infarction. Anaesthesia 2010; 65:733–41
10. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH: Perioperative cardiac events in patients undergoing noncardiac surgery: A review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005; 173:627–34
11. Duvall WL, Sealove B, Pungoti C, Katz D, Moreno P, Kim M: Angiographic investigation of the pathophysiology of perioperative myocardial infarction. Catheter Cardiovasc Interv 2012; 80:768–76
12. Landesberg G: The pathophysiology of perioperative myocardial infarction: Facts and perspectives. J Cardiothorac Vasc Anesth 2003; 17:90–100
13. Devereaux PJ, Sessler DI: Cardiac complications in patients undergoing major noncardiac surgery. N Engl J Med 2015; 373:2258–69
14. Schulman-Marcus J, Feldman DN, Rao SV, Prasad A, McCoy L, Garratt K, Kim LK, Minutello RM, Wong SC, Vora AN, Singh HS, Wojdyla D, Mohsen A, Bergman G, Swaminathan RV: Characteristics of patients undergoing cardiac catheterization before noncardiac surgery: A report from the National cardiovascular Data Registry CathPCI Registry. JAMA Intern Med 2016; 176:611–8
15. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP,

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Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction: Third universal definition of myocardial infarction. Circulation 2012; 126:2020–35

16. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW: Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000; 343:915–22
17. Cohen MC, Aretz TH: Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999; 8:133–9
18. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA: Pathology of fatal perioperative myocardial infarction: Implications regarding pathophysiology and prevention. Int J Cardiol 1996; 57:37–44
19. Berger PB, Bellot V, Bell MR, Horlocker TT, Rihal CS, Hallett JW, Dalzell C, Melby SJ, Charnoff NE, Holmes DR Jr: An immediate invasive strategy for the treatment of acute myocardial infarction early after noncardiac surgery. Am J Cardiol 2001; 87:1100–2, A6, A9
20. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, Lemos PA, Caramelli B: Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: Frequent and dangerous. Atherosclerosis 2012; 222:191–5
21. Parashar A, Agarwal S, Krishnaswamy A, Sud K, Poddar KL, Bassi M, Ellis S, Tuzcu EM, Menon V, Kapadia SR: Percutaneous intervention for myocardial infarction after noncardiac surgery: Patient characteristics and outcomes. J Am Coll Cardiol 2016; 68:329–38
22. Hollis RH, Holcomb CN, Valle JA, Smith BP, DeRussy AJ, Graham LA, Richman JS, Itani KM, Maddox TM, Hawn MT: Coronary angiography and failure to rescue after postoperative myocardial infarction in patients with coronary stents undergoing noncardiac surgery. Am J Surg 2016; 212:814–822.e1
23. Landesberg G, Mosseri M, Wolf Y, Vesselov Y, Weissman C: Perioperative myocardial ischemia and infarction: Identification by continuous 12-lead electrocardiogram with online ST-segment monitoring. Anesthesiology 2002; 96:264–70
24. Landesberg G, Mosseri M, Zahger D, Wolf Y, Perouansky M, Anner H, Drenger B, Hasin Y, Berlatzky Y, Weissman C: Myocardial infarction after vascular surgery: The role of prolonged stress-induced, ST depression-type ischemia. J Am Coll Cardiol 2001; 37:1839–45
25. Raby KE, Barry J, Creager MA, Cook EF, Weisberg MC, Goldman L: Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. JAMA 1992; 268:222–7
26. Landesberg G, Luria MH, Cotev S, Eidelman LA, Anner H, Mosseri M, Schechter D, Assaf J, Erel J, Berlatzky Y: Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 1993; 341:715–9
27. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012; 307:2295–304
28. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery: The Study of Perioperative Ischemia Research Group. N Engl J Med 1990; 323:1781–8
29. Ellis SG, Hertzer NR, Young JR, Brener S: Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol 1996; 77:1126–8

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