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Histological Analysis of Coronary Artery Lesions in Fatal Postoperative Myocardial Infarction

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We sought to evaluate the underlying coronary pathology of fatal postoperative myocardial infarction (MI). It has been hypothesized that most MIs following noncardiac surgery occur in the setting of increased oxygen demand that exceeds coronary blood supply. However, most MIs not associated with surgery are caused by plaque rupture and intracoronary thrombosis. In a retrospective cohort study, we reviewed 1841 consecutive autopsy records from 1981 to 1995 at two institutions and identified 26 cases of postoperative MI with coronary arteries available. Plaque rupture was present in 12 cases (46%, 95% confidence interval [CI] 27%–67%). Of the 9 (35%) patients with intracoronary thrombus, 5 (56%; 19% of entire group) had total occlusion. Thrombus occurred on a >50% stenosis (by cross-sectional area) in a total of 33% (95% CI 16%–55%) of patients. The only statistically significant difference in clinical variables between patients with and without plaque rupture was longer interval from surgery to death in patients with plaque rupture (7.8 ± 4.4 days versus 4.4 ± 4.8 days; $p = 0.047$). In this autopsy series, coronary plaque rupture was associated with almost half of fatal postoperative MI cases. Strategies aimed at reducing triggers of plaque rupture with coronary occlusion might reduce postoperative MI fatality. *Cardiovasc Pathol 1999;8:133–139* © 1999 by Elsevier Science Inc.

Pathological and clinical studies have shown that plaque disruption followed by intracoronary thrombosis is the causative mechanism in 50%–80% of patients presenting with fatal myocardial infarction (MI) or sudden cardiac death (1–4). However, there are little data available showing whether the underlying coronary pathology responsible for postoperative MI is the same or different than MI occurring in other settings (5). Knowledge of the underlying pathoanatomic substrate of culprit coronary lesions in patients with postoperative MI might lead to more effective identification of high-risk patients and better preventive strategies, just as similar knowledge has advanced our treatment of acute coronary syndromes not associated with surgery. We hypothesized that fatal postoperative MI may be associated with plaque rupture similarly to MIs not associated with surgery (1–4,6,7); in other words, the perioperative period may represent a defined trigger for plaque rupture. An alternative mechanism might be oxygen supply–demand mismatch without evidence of an acute coronary event. Therefore, we reviewed the coronary pathology from patients who had suffered fatal postoperative MI in order to estimate the prevalence of plaque rupture.

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Methods

Patients

To identify cases of postoperative MI, we reviewed a total of 1841 consecutive autopsy records at two institutions (Deaconess Hospital, January 1, 1988 to December 31, 1995, $n = 894$; and Lahey-Hitchcock Medical Center, January 1, 1981 to December 31, 1995, ($n = 947$). The study

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was approved by the Institutional Review Boards of both hospitals. We excluded patients who had not received general anesthesia and patients with a history of coronary artery bypass surgery or with postoperative MI complicating cardiac surgery. Of 37 cases of pathologically confirmed postoperative MI identified, 26 had microscopic sections of coronary arteries available and comprised the study population. The medical record of each case was reviewed by one of the investigators (M.C.C.), unaware of the coronary pathology, to obtain patient demographics and clinical characteristics.

We defined any history of coronary artery disease as a history of angina, congestive heart failure, or MI, or Q waves on the electrocardiogram, other abnormal electrocardiogram findings or tests such as a thallium scan suggestive of coronary disease, a positive stress test, or coronary stenoses $\geqslant$50% on previous coronary angiography. A clinically suspected MI was based on typical electrocardiographic or cardiac enzyme changes or on clinical course. Sudden death was defined as unexpected death without preceding symptoms or signs within 24 hours.

Review of pathology specimens was performed by a cardiac pathologist (H.T.A.) who was unaware of the clinical information. All available histological sections of myocardium were examined to confirm the presence of MI and to describe the location of the infarction and its histological characteristics. The histological sections of myocardium were representative in some cases, rather than circumferential. Standard criteria for the diagnosis and age determination of MI were used (8). Myocardial infarctions were classified as acute if specimens showed evidence of myocyte necrosis (e.g., hypereosinophilia, contraction band necrosis, wavy fibers) with or without an infiltrate of polymorphonuclear leukocytes. Healing MIs contained a predominantly chronic inflammatory infiltrate (e.g., macrophages, lymphocytes, plasma cells), beginning collagen deposition, and neovascularization. Healed MIs showed dense, well-established collagen deposition with little remaining inflammatory infiltrate. Areas of fibrosis described grossly were also included as healed MIs even if not confirmed microscopically. Microscopic confirmation was required for the diagnosis of acute and healing MIs. Infarctions of varying age were observed in some patients. The most recent MI (8) was used as the index MI.

The pathologist also reviewed the serial histological sections of the coronary arteries for the presence of plaque cap fissuring (i.e., disruption of the fibrous cap), plaque hemorrhage, or luminal thrombus containing plaque elements (e.g., cholesterol crystals and lipid-laden macrophages), which we defined as evidence of plaque rupture. We defined significant coronary stenosis as $\geqslant$50% reduction in luminal area.

Statistical Analysis

All results are expressed as mean $\pm$ standard deviation or as a percentage for continuous and categorical variables, respectively. Normally distributed continuous variables were compared using an unpaired *t* test. Non-normally distributed continuous variables were compared using the Wilcoxon rank sum test. Categorical variables were analyzed using the Fisher exact test. Binomial exact 95% confidence intervals (95%CI) are presented when appropriate. Statistical significance was established at two-sided $p < 0.05$.

Results

We identified 26 patients (age 68 $\pm$ 13 years; 9 females) who had suffered a fatal postoperative MI whose coronary histology was available for review. All MIs appeared to be $\leqslant$72 hours in age. Fatal MI complicated the following types of surgical procedures: general surgery (10), vascular surgery (9), thoracic surgery (4), orthopedic surgery (2), and neurosurgery (1). Surgery was elective in all but one case. Death occurred a mean of 6.0 $\pm$ 4.9 (range, 0 to 17) days after surgery. Within the entire group, 21 patients (81%) had pathological evidence of old left ventricular MI compared with a clinical history of prior MI in only 5 patients (19%). A total of 9 patients (35%) had new right ventricular infarction. Multivessel coronary artery disease was present in 23 patients (88%); 6 patients (23%) had left main coronary artery disease. The distribution of coronary involvement is summarized in Table 1. The distribution of sites of new left ventricular MI was as follows: circumferential (19%), septal (4%), anteroseptal (4%), anterior (4%), anterolateral (4%), lateral (8%), posterolateral (12%), and multiple sites (35%). Myocardial infarction was transmural in 62% (95% CI, 41%–80%) of cases.

Evidence of plaque rupture was present in 12 patients (46%; 95% CI, 27%–67%). Figure 1 shows a typical coronary artery with evidence of plaque rupture. Table 2 summarizes patient characteristics and pathological findings in patients with and without plaque rupture. The single patient who underwent emergency surgery (undertaken for a leaking abdominal aortic aneurysm) was female, had a history of coronary artery disease, suffered a new transmural MI, and showed evidence of plaque rupture. There was no statis-

Table 1. Distribution of Coronary Artery Disease in Patients With Fatal Postoperative Myocardial Infarction

	n (%) ($n = 26$)
Coronary artery	
Left main coronary artery	6 (23)
Left anterior descending coronary artery	21 (81)
Left circumflex coronary artery	19 (73)
Right coronary artery	20 (77)
Number of vessels diseased (excluding left main coronary artery)	
1	1 (4)
2	8 (31)
3	14 (54)

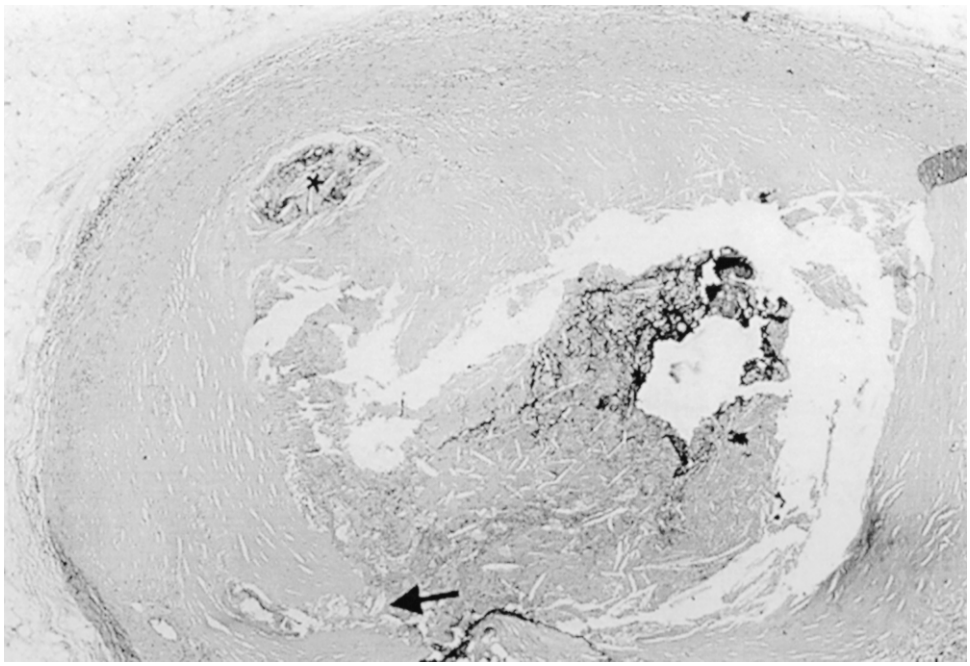

Figure 1. Low-power photomicrograph showing an example of a ruptured plaque in one of the cases. The *arrow* points to the breach in the fibrous cap, and the lumen contains a recent thrombus with cholesterol clefts, typical of plaque rupture and thrombosis. There is also a focus of plaque hemorrhage (*).

Table 2. Clinical and Pathological Characteristics

Variable	No Plaque Rupture (n = 14) (%)	Plaque Rupture (n = 12) (%)	p
Clinical variables			
Age (y)	65.1 ± 13.6	70.8 ± 12.9	0.29
Male gender	9 (64)	8 (67)	1.00
Any history of CAD	9 (64)	8 (67)	1.00
History of MI	3 (21)	2 (17)	1.00
Interval to death (days)	4.4 ± 4.8	7.8 ± 4.4	0.047
Operative fluids (cc)	1718 ± 1776	1882 ± 1743	0.78
Postoperative fluids days 1–3 (cc)	3133 ± 1320	5014 ± 4940	1.00
Fluids 24 hours preceding death (cc)	1407 ± 1351	2030 ± 2793	0.86
Clinical MI	6 (43)	5 (42)	1.00
Sudden death	8 (57)	6 (50)	1.00
CPR	11 (79)	7 (58)	0.40
Cardioversion	10 (71)	5 (42)	0.23
Beta-blocker 24 hours preceding death	2 (14)	3 (25)	0.63
Pressors	13 (93)	11 (92)	1.00
Pathological variables			
Old MI	10 (71)	11 (92)	0.33
Transmural MI	6 (46)	10 (83)	0.097
Old RVMI	4 (33)	4 (40)	1.00
New RVMI	5 (42)	4 (40)	1.00
Thrombus on ⩾ 50% stensois	1 (8)	7 (64)	0.008
Multivessel CAD	12 (86)	11 (92)	0.86

Note: some data missing for some patients.

Abbreviations: CAD = coronary artery disease (defined as a history of angina, congestive heart failure, or myocardial infarction, or Q waves on the electrocardiogram, other abnormal electrocardiogram findings or tests such as a thallium scan suggestive of coronary disease, a positive stress test, or coronary stenoses ⩾50% on previous coronary angiography); CPR = cardiopulmonary resuscitation; MI = myocardial infarction (clinical MI = clinically suspected myocardial infarction based on the electrocardiogram, cardiac enzymes, or clinical course); Pressors = medications to increase heart rate or blood pressure (e.g., dopamine, epinephrine, and phenylephrine); RVMI = right ventricular myocardial infarction.

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tically significant difference in the presence or absence of plaque rupture among patients with circumferential (8% versus 29%; $p = 0.33$) or multiple MIs (29% versus 42%; $p = 0.68$).

Intracoronary thrombus was seen in a total of 9 (35%; 95% CI, 17%–56%) patients. In 8 of these 9 cases, the thrombus was present at the site of an atherosclerotic plaque that occluded ⩾50% of the luminal diameter. This represents 31% (95% CI, 16%–55%) of all patients. We observed intracoronary thrombus completely occluding the lumen in 5 patients. This accounts for 19% of all cases and 56% of the 9 cases in whom any thrombus was visible. Thrombus was seen in 8 of the 16 patients with pathologically confirmed transmural MI compared with none of the remaining 10 patients ($p = 0.052$).

The only statistically significant difference in clinical variables between patients with and without plaque rupture was longer interval from surgery to death in patients with plaque rupture (7.8 ± 4.4 days versus 4.4 ± 4.8 days, $p = 0.047$) (Figure 2). Fewer than half of all patients (12/26) received intravenous pressors within 48 hours of death, not associated with terminal resuscitative efforts. Just over half of these patients had evidence of plaque rupture (7/12; $p = 0.70$).

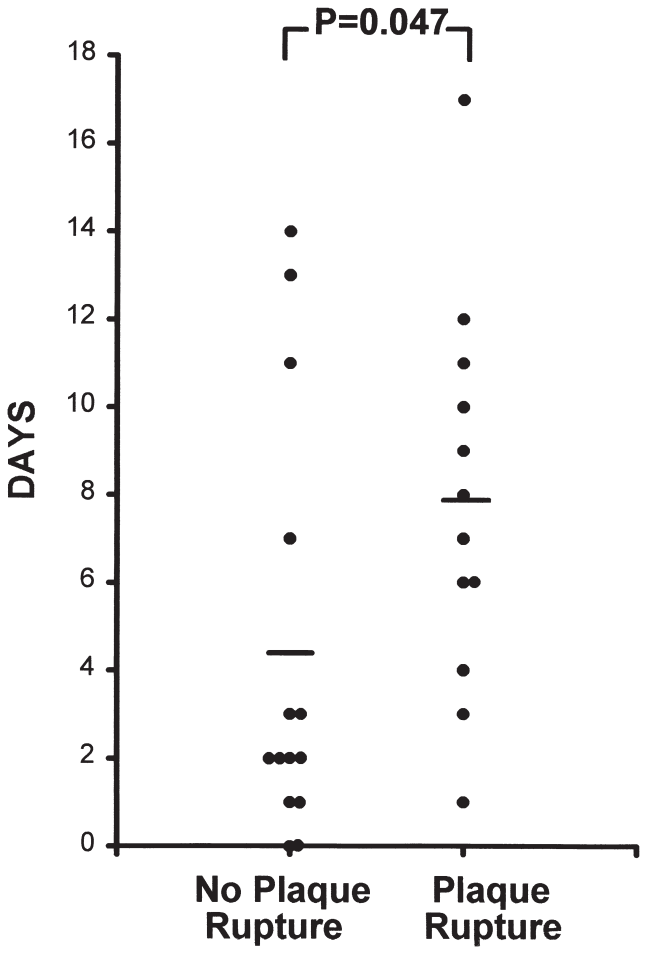

Figure 2. Interval from surgery to death in patients with and without plaque rupture. The *dark horizontal bar* indicates the mean for each group.

Discussion

In this study of patients with fatal postoperative MI, we identified signs of plaque rupture in nearly half of cases. The morphology of coronary lesions and incidence of plaque disruption that we observed is similar to previous studies of sudden cardiac ischemic death (1–4,6,7) in which close serial sections of coronary arteries were examined. Thus, fatal postoperative MI may have similar pathophysiologic mechanisms of onset as MI not associated with surgery.

Our findings confirm those of Dawood and colleagues (9) who found evidence of plaque rupture in 23 (55%) of 42 (95% CI, 39%–70%) patients who died following noncardiac surgery in two institutions. These authors also found a similar incidence of plaque rupture in patients who had fatal nonoperative MI (10 [40%] of 25 patients; 95% CI, 21%–61%). Results of previous studies of plaque rupture are summarized in Figure 3.

Studies of perioperative MI have shown that risk peaks within the first 3 postoperative days (10,11). Most postoperative MIs are non–Q-wave and are detected in the first 24 postoperative hours. This is likely due to increased surveillance with frequent electrocardiograms and cardiac enzymes (12–14). Studies using perioperative Holter monitoring suggest that postoperative adverse cardiac events are preceded by tachycardia and electrocardiographic evidence of ischemia, frequently within the first 3 postoperative days (12,15–19). A recent angiographic study identified collateral vessels inadequate to prevent MI during surgical stress, and the number of coronary lesions with >30% stenosis correlated with postoperative MI or death (20). Interventions aimed at increasing oxygen supply—through increased oxygen delivery (21) or improved blood flow via intraaortic balloon counterpulsation (22) or coronary revascularization (23,24)—are associated with decreased postoperative cardiac morbidity and mortality.

These data support the theory that oxygen supply and demand mismatch may cause postoperative cardiac events. This mechanism may have played a role in the circumferential infarctions noted in our study. Thus, the current practice of preoperative risk assessment with methods that detect fixed intracoronary lesions such as stress thallium scanning or stress echocardiography has a rational basis. However, these data do not provide enough evidence to exclude plaque rupture as a possible etiology (5).

Several groups of investigators (25–30) have demonstrated fibrinolytic shutdown and the existence of a postoperative hypercoagulable state. Additionally, there is a surge in catecholamine levels after noncardiac surgery (31–36). These postoperative neurohumoral changes may cause perioperative myocardial ischemia via an increase in oxygen

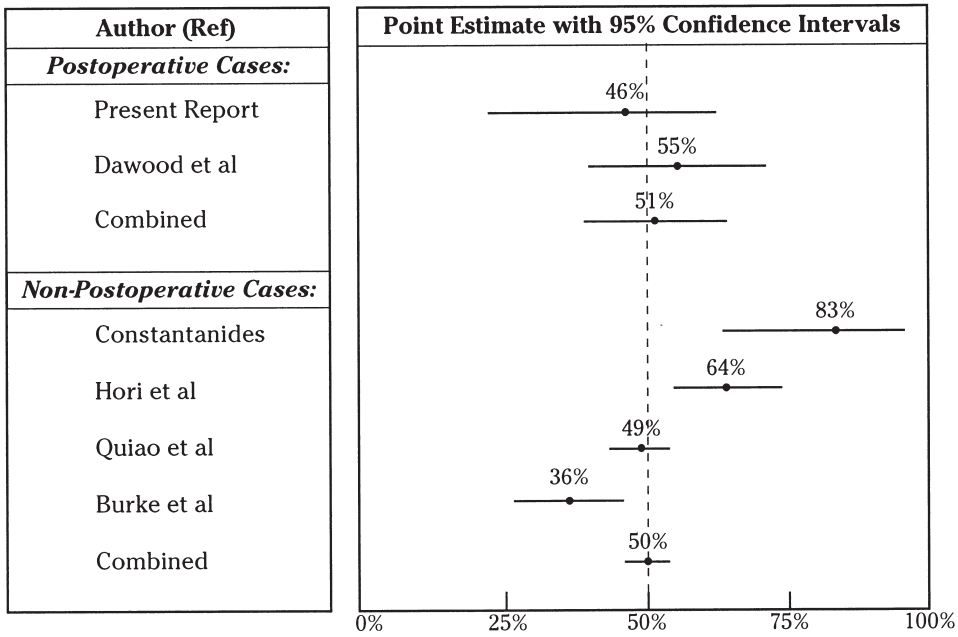

Figure 3. The incidence of plaque rupture in studies of fatal postoperative myocardial infarction and sudden ischemic cardiac death not associated with noncardiac surgery. Note that pooled point estimates of the incidence of plaque rupture are not statistically significantly different (51% versus 50%, $p = 0.90$) and that confidence intervals overlap.

demand from catecholamine-induced increases in heart rate and blood pressure, a decrease in myocardial oxygen supply from coronary vasoconstriction mediated by catecholamine stimulation of $alpha_1$-adrenergic receptors, and a postoperative prothrombotic milieu (37). Such a milieu may explain the high incidence of plaque rupture with thrombosis and resulting transmural MI that we observed compared with previously reported clinical studies (12–14). This milieu may also account for the relative delay in fatality compared to non–Q-wave MI. It may take days of increased shear forces from tachycardia to destablize an intracoronary plaque, resulting in coronary thrombosis.

Although 19% of MIs were circumferential, possibly related to a diffuse oxygen supply and demand mismatch, plaque rupture with coronary thrombosis is not necessarily excluded as a mechanism of fatal MI in any particular patient, as evidenced by the observation that one of these patients demonstrated plaque rupture. Subendocardial infarction, seen at the time of autopsy, may have been subsequent to or initiated by plaque rupture. Similarly, because mechanisms of MI (i.e., oxygen supply and demand mismatch and plaque rupture) are not mutually exclusive, MI in multiple locations may be possible in a given patient.

Our findings indicate that plaque rupture with coronary thrombosis may be an important cause of fatal postoperative MI. Along with evidence that nonfatal MI may be caused by oxygen supply and demand mismatch, these findings suggest that multiple strategies are likely required to maximally achieve reduced perioperative cardiac risk. Selective preoperative screening with stress imaging and subsequent revascularization may have short-term and long-term benefits (38). Other strategies might include the use of anesthetic agents such as fentanyl that block afferent pain signals, which might blunt postoperative catecholamine surges (39), and epidural anesthesia used to decrease postoperative pain, which may achieve the same effect (40). $Alpha_2$-adrenergic blockers may be useful in the perioperative period to blunt intraoperative hypertension and tachycardia (41–43) or the postoperative surge in catecholamines (41). Continuous real-time electrocardiographic monitoring may enable early detection of tachycardia and ischemia. More widespread use of perioperative beta blockade (44–47) may prevent adverse postoperative cardiac events by decreasing myocardial oxygen demand or by inhibiting plaque rupture. Nitrates may counteract catecholamine-induced coronary vasoconstriction (48,49). Low-dose heparin or aspirin may counteract the postoperative prothrombotic state and attenuate the clinical effects of plaque rupture later in the hospital stay.

There are several limitations to this study. Our methodology (i.e., review of autopsy specimens) was inherently insensitive for detection of plaque rupture compared with more rigorous investigations of plaque disruption using serial sections of prospectively obtained specimens. We relied on review of myocardial and coronary pathology sectioned according to clinical practice. That thrombus was noted in one patient without evidence of plaque rupture indicates that the site of plaque disruption may have been missed during sectioning. Underestimation of the incidence of thrombus formation may have occurred because of spontaneous fibrinolysis that is known to occur even within 24 hours of symptom onset (50). Nevertheless, evidence of plaque rupture was observed in nearly half of cases with confidence intervals that overlap the results of previous reports.

The coronary arteries were not perfused at postmortem examination, and morphometric estimates of stenoses were made using formalin-fixed specimens. Because the coro-

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nary arteries were not distended when fixed, stenosis severity may have been overestimated. We considered ⩾50% reduction of coronary artery luminal area as a histological marker of significant atherosclerosis.

We did not analyze the relationship between time from MI to death because it is not possible to establish the exact time of infarction from our retrospectively collected data. Likewise, as a retrospective study, postoperative electrocardiograms and cardiac enzymes were not available for all patients because these tests were performed only if clinically indicated, and because risk factors for coronary artery disease were not reliably recorded.

We acknowledge that "demand" and "supply" infarctions may not be unrelated in etiology. The postoperative phase may be the trigger for both increased oxygen-demand infarctions (in the setting of fixed stenoses) and decreased blood supply (plaque rupture and thrombosis) via similar pathophysiology (i.e., increased catecholamines). The pathological findings in the two groups that we observed may thus simply reflect a difference in response and not a difference in etiology. Additionally, this study was not designed to define other potential pathophysiologic mechanisms of postoperative myocardial infarction.

As an autopsy study, selection bias may also affect results. The cases that have postmortem examination might or might not be a representative sample of total postsurgical deaths, which in turn are a fraction of all postoperative cardiac morbidity. More severe coronary atherosclerosis may have been observed in this group of patients with fatal postoperative MI, and these results should not be extrapolated to patients with nonfatal postoperative MI.

Conclusions

In this autopsy study, plaque rupture in coronary arteries was associated with almost half of fatal postoperative MI cases. Despite a relatively insensitive methodology, our results are consistent with the findings of other investigations of sudden ischemic cardiac deaths not associated with surgery. Further prospective investigations, including randomized controlled clinical trials, are necessary to define the mechanisms and optimal, cost-effective, preventive strategies for adverse postoperative cardiac events.

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