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EDITORIAL COMMENT

Surgery Casualties

Do Not Leave Hearts Behind Enemy Lines*

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Winning battles sometimes leave innocent bystanders wounded or even killed on the ground. Although a surgical intervention may be successful in treating a diseased organ, it may affect the heart, resulting in ischemia, infarction, or life-threatening dysrhythmias. The disease is conquered, but the patient may die of a de novo or decompensated heart disease.

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Weiser et al. (1) recently estimated that 234 million major surgical procedures are performed every year worldwide. An exaggerated neuroendocrine and sympathetic response as part of the stress response to anesthesiology and surgical maneuvers, as well as the inflammatory and hypercoagulable state induced by surgery and transient hypoxia elicited by anesthesia/analgesia, hypothermia, and bleeding or anemia, can unmask latent coronary artery disease, triggering thrombotic and ischemic events in the patient at risk (2). The same pathophysiological triggers may account for other life-threatening cardiovascular events, such as acute decompensated heart failure and major arrhythmias.

Cardiovascular events are severe and frequent complications during noncardiac surgery (2–4), with a major cardiac event occurring in either 3.9% of patients with or at risk of cardiac disease or in 1.4% of unselected patients (2). A recent large (n = 15,133) prospective study evaluating post-operative high-sensitivity cardiac troponin T levels and 30-day mortality after noncardiac surgery revealed that an elevation greater than the 99th percentile was present in 12% of subjects (5). A high-risk type of procedure matters: the incidence of perioperative myocardial ischemia and infarction in vascular surgery ranged from 14% to 47% and from 1% to 26%, respectively, in 13 studies published from 2000 to 2010 evaluating myocardial damage using either cardiac troponin I or T (6).

Although the perioperative event rate has decreased over the past 30 years as a consequence of improvement in anesthesiology and surgical techniques, perioperative cardiac complications remain a significant problem, whereas the most widely accepted current risk prediction model, the Revised Cardiac Risk Index (7) (based on the type of surgery; history of cardiac, cerebrovascular, or kidney disease; and pre-operative treatment with insulin), has recognized limitations (8,9).

The use of cardiac biomarkers in clinical settings that put patients at risk for cardiac events has been successful in improving risk stratification, guiding medical decision making, and preventing cardiac disease progression. This is the case in patients with neoplastic disease receiving potentially cardiotoxic drug treatment, in whom the combination of screening by troponin assay and biomarker-oriented use of angiotensin-converting enzyme inhibitors has been proven effective (10). The prognostic value of cardiac biomarkers in patients undergoing noncardiac surgery is supported by growing evidence. The post-operative troponin T level is associated with an outcome with graded response, with up to a 16.9% 30-day mortality in those with a troponin T level >0.30 ng/ml (2). Increasing troponin I, assayed by a regularly scheduled post-operative protocol, showed a 3-fold increase in the probability of detecting myocardial injury, compared with clinically based measurements, and a dose-response association with increased mortality in moderate- to high-risk patients in a retrospective cohort analysis of 51,701 consecutive patients (11). Conversely, elevated pre- and post-operative B-type natriuretic peptide (NP) concentrations have been shown to be powerful independent predictors of perioperative cardiovascular complications (i.e., mortality, myocardial infarction, and heart failure) (12,13).

However, most recent guidelines are controversial in regard to the use of biomarkers in the setting of noncardiac surgery. The 2007 National Academy of Laboratory Medicine Guideline has suggested the perioperative assay of troponins to detect silent ongoing heart damage or for post-operative risk stratification in high-risk subsets, such as those undergoing vascular surgery, and denied evidence to recommend the routine measurement of brain natriuretic peptide (BNP) and N-terminal fragment of proBNP (NT-proBNP) before or after cardiac surgery (14). This indication is debated by the 2009 American College of Cardiology Foundation/American Heart Association guidelines (15), which restricted troponin use to patients with electrocardiographic changes and chest pain. European 2009 guidelines did not recommend routine biomarker sampling to prevent cardiac events among patients undergoing noncardiac surgery (3), whereas pre-operative measurement of BNP or NT-proBNP was recommended to obtain prognostic information on perioperative and late cardiac events in high-risk patients (3).

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In this issue of the *Journal,* Rodseth et al. (16) have evaluated whether the measurement of post-operative BNP and NT-proBNP levels enhance risk stratification in adult patients undergoing noncardiac surgery, compared with a single pre-operative BNP and NT-proBNP assay or the delta of concentration. Rodseth et al. (16) conducted a meta-analysis, including individual data of 2,179 patients from 18 eligible studies, to determine whether the addition of post-operative BNP or NT-proBNP values enhanced the prediction of the composite of death and nonfatal myocardial infarction at 30 and ≥180 days after surgery. They found that post-operative BNP and NT-proBNP were the strongest independent predictors of the primary outcome and provided an additive value to a risk prediction model containing pre-operative assays, improving model fit and risk classification.

Cardiac NPs, which include BNP and its related peptide NT-proBNP, constitute a complex family of peptide hormones produced and secreted by the human heart (17). Under physiological conditions, ventricular myocardium produces only a limited amount of BNP; conversely, several pathophysiological mechanisms, some associated with chronic disease (e.g., ventricular hypertrophy/fibrosis and left ventricular systolic/diastolic dysfunction) and transient conditions, such as those occurring during surgery stress (e.g., inflammation and myocardial ischemia/hypoxia), stimulate BNP production and release from ventricular cardiomyocytes (17). International guidelines recommend the measurement of BNP for the diagnosis, risk stratification, and follow-up of patients with chronic or acute heart failure (18), as well as for risk assessment in patients with symptoms consistent with acute coronary syndrome (19).

Rodseth et al. (16) are to be congratulated for their successful effort. Their findings may affect future patient management. The predictive value of the level of post-operative B-type NPs might reflect the influence of procedural maneuvers and cardiac/systemic complications after surgery and may be used to identify a subset of patients at major risk, requiring enhanced diagnostic and therapeutic effort. However, there are still relevant issues to be solved. Is the prognostic value of an early increase of troponins or NP concentration after noncardiac surgery (<3 days) independent and additive? Although a single report seems to be negative in this respect (20), Rodseth et al. (16) have a database with individual data containing both troponin and NP and may be able to give a preliminary answer to this crucial question. Yet, an early concomitant elevation of either biomarker could recognize the same ischemic trigger and provide only redundant information. Conversely, at least a subset of patients with post-operative negative troponin might show an NP increase due to nonischemic determinants. Because the clinical value of a marker/multimarker strategy should be assessed by its effect on patient management and outcomes, in this instance, diagnostic decision making should consider possible ongoing, life-threatening noncoronary pathologies (e.g., acute decompensated chronic heart failure and pulmonary embolism), with adoption of specific therapeutic options, likely different from those recommended for preventing ischemic events (i.e., continuation of chronic titrated cardioselective beta-blocker, statin, and aspirin treatment).

Surgeons, anesthesiologists, and clinicians should hear their patient's heart whispering its silent pain and damage while secreting its hormones and releasing proteins into the bloodstream. However, to improve perioperative risk stratification in noncardiac surgery, and going beyond established clinical scores with the use of cardiac biomarkers, prospective studies are needed, specifically aimed at evaluating the independence of troponin and NP predictive value even in mid- and long-term periods, and at assessing the usefulness of NP levels as a guide to therapy affecting prognosis.

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Key Words: natriuretic peptides ■ perioperative myocardial infarction ■ perioperative risk ■ surgery.