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Assessment of Preoperative B-Type Natriuretic Peptide in Adult Surgeries: Is It Useful?

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B-type natriuretic peptide (BNP) is secreted primarily by ventricular myocytes in response to increased wall stress induced by volume expansion, pressure overload, or ischemia of the cardiac chambers.¹ Elevated plasma BNP is a proven diagnostic and prognostic biomarker in the setting of ambulatory heart failure and acute coronary syndromes.^{2–5} With BNP established as clinically relevant in nonsurgical cohorts, efforts have moved to determining whether preoperative BNP can be used to improve risk stratification of surgical patients. This interest is prompted by the fact that the majority of significant postoperative complications are cardiovascular.⁶ Worldwide, about 200 million noncardiac surgeries are performed annually, with conservative estimates indicating approximately 1 million accompanying adverse postoperative cardiac events.^{7,8} Surgical risk models that use patients' clinical risk factors alone miss a sizeable proportion of patients who go on to develop adverse postoperative cardiovascular events.⁹ Furthermore, the American College of Cardiology/American Heart Association's perioperative guidelines strongly emphasize patients' functional status when determining who warrants preoperative cardiac testing, yet surgical patients are frequently elderly and have limited preoperative physical activity levels.¹⁰

A preoperative biomarker test, therefore, could prove very useful for surgical risk stratification and perioperative patient care if it is easy and inexpensive to measure, is sensitive and specific for cardiac pathology and adverse postoperative cardiovascular outcomes, adds to what can be anticipated using clinical criteria or routine cardiac testing, and can be used to direct perioperative management changes to improve patient outcomes. Several meta-analyses of studies of noncardiac surgical patients have shown that elevated preoperative BNP or N-terminal proBNP (NT-proBNP) is strongly associated with adverse short^{11–13} and longer term¹³ postoperative major adverse cardiovascular events and

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mortality. Furthermore, the meta-analysis by Lurati Buse et al. in this issue of *Anesthesia & Analgesia* illustrates that elevated preoperative BNP is associated with all-cause mortality in both noncardiac and cardiac surgical patients, with BNP thresholds providing high negative predictive value in both surgical groups.¹⁴ What remains to be delineated is precisely how physicians and patients should interpret and use preoperative BNP measurements for perioperative planning to prevent adverse postoperative patient outcomes.

Although there are strong associations between elevated circulating BNP and the development of adverse outcomes after surgery, a major challenge facing the use of BNP for surgical risk stratification and patient care lies in identifying useful preoperative BNP thresholds or cut-points above which a patient is deemed “at risk.” There is substantial heterogeneity in the BNP thresholds described in the studies reporting significant associations between elevated preoperative BNP and adverse postoperative outcomes.^{11–14} Potential reasons for this heterogeneity include variability in commercially available BNP assays as well as between study differences in the types of surgical patients assessed (i.e., differences in overall cardiovascular health of studied surgical cohorts).

NT-proBNP has a longer half-life than does BNP, so its levels are elevated when compared with a BNP measurement performed on the same blood sample.¹⁵ Additionally, there are multiple commercially available assays for measuring both BNP (active fragment) and NT-proBNP (inactive fragment), with some between-assays variability.¹⁶ Cut-points identified in the literature for clinical use should therefore be considered specific to the assessed BNP assay. Also contributing to variability in reported BNP risk thresholds is the fact that BNP (or NT-proBNP) is elevated in the setting of even subtle myocardial stress or failure and becomes progressively more elevated as myocardial stress increases. Therefore, the normal range of BNP varies according to surgical population (i.e., preoperative BNP levels will differ according to the cardiac disease burden of specific surgical populations). For example, this is why aortic valve replacement patients generally have higher preoperative BNP values than do patients undergoing isolated coronary artery bypass grafting, or why vascular surgical patients (who often have coronary artery disease) generally have higher preoperative BNP values than do healthy day-surgery patients.^{11–14,17–19} To be useful for diagnosing and prognosticating, one may need to establish different preoperative BNP risk thresholds for different surgical populations, with studies focusing on surgical cohorts characterized by general homogeneity of the invasiveness of the surgeries included, as well as the degree of enrolled subjects’ typical preoperative cardiac pathology. The ongoing multicenter VISION Study (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study) is on target to enroll 40,000 noncardiac surgical patients, and will evaluate NT-proBNP for association with postoperative adverse cardiovascular events. This effort in noncardiac surgical patients will provide well-powered analyses of surgery-specific subcohorts.

In this issue, Lurati Buse et al.’s meta-analysis illustrates that overall, in studies of all-cause mortality in both noncardiac and cardiac surgical cohorts, preoperative BNP risk thresholds demonstrate high negative predictive value, but substantially lower positive predictive value.¹⁴ In other words, although preoperative BNP risk thresholds tend to exclude patients who are likely to die after surgery, having a BNP value above the risk threshold may or may not mean that a patient has a heightened risk of mortality. However, BNP is a biomarker of

subclinical and clinical heart failure. Therefore, from a biological standpoint, elevated preoperative BNP is most likely to be associated with postoperative morbidity and mortality related to heart failure or, possibly, myocardial infarction. Studies assessing all-cause mortality will include patients as having the study outcome if they died from cardiac causes. However, an all-cause mortality outcome will not capture patients who suffer from postoperative heart failure but who do not die during the study period. Furthermore, many studies assessing postoperative major adverse cardiovascular events do not include heart failure in the composite outcome.¹² Future studies focused on the hypothesis that elevated preoperative BNP predicts occurrence of postoperative heart failure—specific events may identify improvement in the positive predictive value of the BNP test. Additionally, the negative predictive value of a test will be higher when assessed in surgical cohorts at a generally low risk of developing the adverse outcome being tested for. Preoperative BNP is most likely to be useful for identifying potential cardiovascular problems not in the lowest-risk patients and not in the very highest risk patients (i.e., the patients with obvious clinical symptoms of cardiac disease), but in those surgical patients with moderate potential for cardiovascular complications. Therefore, it is most valuable to know the negative predictive value of preoperative BNP risk thresholds in moderate-risk surgical cohorts.

In cardiac surgical patients, postoperative C-reactive protein and cardiac troponin I measures have been shown to add to postoperative BNP's ability to predict major adverse cardiovascular events occurring up to 1 year after surgery, but the authors did not similarly evaluate these biomarkers preoperatively.²⁰ Emerging heart failure biomarkers such as ST2, a member of the interleukin 1 receptor family, appear to augment what can be predicted in chronic heart failure patients using BNP alone.²¹ Future studies could evaluate whether assessment of multiple preoperative biomarkers could improve preoperative surgical risk assessment and the positive predictive value provided by BNP testing alone. Furthermore, increasingly sophisticated statistical methods are being used to evaluate optimal biomarker risk thresholds. Use of 2 pronged approaches of receiver operating characteristic curve and net reclassification index methods may improve the ability to identify preoperative BNP risk thresholds with the best balance between positive and negative predictive values.²²

What is particularly appealing about evaluating preoperative BNP is its potential to be used to guide clinical care to improve patient outcomes. Although there have been no studies of BNP-guided perioperative management, it seems logical that patients with elevated preoperative BNP, particularly patients with no known contributing cardiac pathology, should undergo further cardiac evaluation, possibly including echocardiography, stress tests, and coronary angiography. This could allow otherwise undetected coronary artery disease or cardiac valve disease to be addressed prior to surgery. At a minimum, the anesthesiologist could be aware of significant cardiovascular abnormalities—such as coronary artery disease, cardiac valve disease, pulmonary hypertension, or low left ventricular ejection fraction—and could plan anesthetic management accordingly. Also, if patients and surgeons know of added risk of cardiac complications, they might be inclined to forgo an elective surgery or to choose a more conservative but less invasive surgical approach. Furthermore, patients with elevated preoperative BNP secondary to subclinical or clinical heart failure could potentially be medically optimized before and after surgery, with progress in this optimization evaluated using serial BNP measurements. Studies of ambulatory heart failure patients have found that

medical management guided towards decreasing serial follow-up BNP or *N*-terminal proBNP measures (i.e., aggressive titration of medications including β -blockers and angiotensin converting enzyme inhibitors) is associated with improved heart failure readmission-free survival.^{23–25} It is conceivable that surgical patients with elevated preoperative BNP may have fewer adverse postoperative cardiac events (particularly heart failure events) with similar models of pre- and postoperative surveillance.

Anesthesiologists and other perioperative clinicians work daily to try to identify patients who might benefit from even closer preoperative or postoperative surveillance and intervention. With regard to understanding how assessment of preoperative BNP might aid in this endeavor, the first step has clearly been established. Elevated preoperative BNP strongly associates with adverse postoperative outcomes, even after adjusting for important clinical risk factors such as low preoperative left ventricular ejection fraction,^{12,17,19} yet it is the next steps that will determine how BNP measurements can best be used to help surgical patients. Clinical investigators need to identify preoperative BNP risk thresholds that are specific for predicting outcomes such as postoperative heart failure or myocardial infarction in surgery-specific cohorts. Once these thresholds are established, further research can determine the most important step, which will be to establish the efficacy of BNP-guided interventions to reduce adverse postoperative cardiac events.

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