Perioperative B-type Natriuretic Peptide/*N*-terminal pro-B-type Natriuretic Peptide

Next Steps to Clinical Practice

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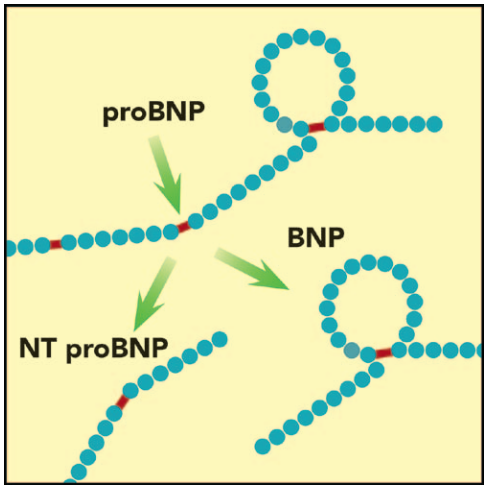
THE heart is not only a pumping organ but also an endocrine organ. B-type natriuretic peptide (BNP) is secreted primarily by cardiac ventricular myocytes in response to increased ventricular wall stress induced by volume expansion, pressure overload, or ischemia.[1] BNP protein formation begins with intracellular translation into a large preprohormone that is processed to pro-brain natriuretic peptide (proBNP) and then is cleaved and released into the circulation as active BNP and biologically inactive *N*-terminal proBNP (NT-proBNP) fragment.[1] Commercial assays are available to measure circulating BNP and NT-proBNP. Although BNP has known compensatory natriuretic, diuretic, and vasodilatory properties, studies of both ambulatory and surgical patients have found that elevations of circulating BNP or NT-proBNP significantly associate with increased adverse cardiac events.[1–3] Worldwide, approximately 200 million noncardiac surgeries are performed every year, with 30-day postoperative mortality estimated at approximately 2%.[4,5] A number of studies therefore have evaluated whether elevations in preoperative BNP or NT-proBNP predict cardiac morbidity and mortality after noncardiac surgeries. In this issue of Anesthesiology, Potgieter *et al.*[6] provide an elegant comparison of two different approaches to meta-analysis of 14 studies of noncardiac surgical patients (n = 2,196) that assess the association between elevated preoperative NT-proBNP and the composite outcome of 30-day postoperative mortality or nonfatal myocardial infarction (MI). The authors report that meta-analysis that aggregates study findings using the different optimal cut-points and corresponding odd ratios (ORs) established for each individual study cohort (*i.e.*, aggregate data approach) results in a substantially inflated reported OR for association between NT-proBNP and 30-day postoperative outcome when compared with meta-analysis that combines individual-level data across all studies to define one optimal NT-proBNP cut-point to be used across all study cohorts (*i.e.*, individual patient-level data approach). These findings provide an important warning regarding likely overestimation of effect size reported in aggregate data meta-analyses of biomarker studies. However, although the results of the individual patient-level data meta-analysis by Potgieter *et al.* demonstrate a marked shrinkage in resulting OR from the OR identified using aggregate data meta-analysis, their findings still highlight a clinically relevant effect size (OR for association between NT-proBNP >367.15 pg/ml and 30-day outcome = 3.61; 95% CI, 2.73 to 4.78). Thus, the question remains regarding what next studies and steps can be undertaken to determine whether perioperative NT-proBNP or BNP assessments can be used in clinical practice to predict and mitigate postoperative morbidity and mortality.



"… to move BNP and NT-proBNP assessment into perioperative clinical practice, useful cut-points or risk thresholds must be identified."

A key impediment to moving evaluation of perioperative BNP or NT-proBNP into routine clinical practice for risk stratification and management of surgical patients is the lack of clarity from presently available literature regarding what cut-points of these biomarkers should be used to determine the risk. Several factors contribute to this lack of clarity. First, although both elevated BNP and NT-proBNP associate with adverse cardiovascular outcomes in ambulatory and surgical cohorts,[1–3] NT-proBNP has a longer half-life than BNP and typically has two- to three-fold higher circulating concentrations than BNP. For clinical use, any cut-points identified in the literature should be considered specific to the BNP or NT-proBNP assay that was used. Second, BNP and

Image: A. Johnson.

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NT-proBNP are increasingly elevated along the spectrum from subclinical heart disease to fulminant clinical cardiac decompensation. Patients presenting for one type of surgery are not necessarily like patients presenting for another type of surgery with regard to overall presenting burden of cardiovascular pathology. Magnitude and range of preoperative BNP or NT-proBNP concentrations will differ according to the presenting cardiac disease burden of different surgical groups. For example, aortic stenosis patients generally will have higher BNP or NT-proBNP concentrations than primary coronary artery bypass graft (CABG) patients, and vascular surgical patients (likely high incidence of coronary artery disease) generally will have higher BNP or NT-proBNP concentrations than healthy day-surgery patients.

So to identify clinically relevant BNP or NT-proBNP cut-points for potential use in risk assessment and management of surgical patients, these cut-points need to be established for specific types of surgeries. One way to accomplish this is to identify assay-specific cut-points associated with adverse postoperative outcomes by doing large prospective observational studies of specific surgical groups (*e.g.*, higher-risk noncardiac surgery *vs.* primary CABG surgery *vs.* aortic valve replacement, and more). Ideally, each cut-point is then validated in additional large surgical cohorts. Large multicenter collaborative studies such as the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study (ClinicalTrials.gov, NCT00512109) will make this approach possible for certain subgroups of noncardiac surgeries. However, feasibility, time, and cost are significant deterrents to the large, surgery-specific discovery and validation cohort study approach for identification of biomarker cut-points.

The results of the individual patient-level data meta-analysis of NT-proBNP by Potgieter *et al.* suggest that this meta-analysis approach could provide an alternate approach for identifying the usable perioperative biomarker cut-points. The individual patient-level data meta-analysis by Potgieter *et al.* demonstrated a clinically relevant OR for association between preoperative NT-proBNP and 30-day mortality or MI, but their findings are also potentially useful because this OR was derived from studies that include a grouping of higher-risk noncardiac surgeries: thoracic, vascular, urology, orthopedic, and general surgery with known coronary artery disease or multiple cardiac risk factors. Based on the findings by Potgieter *et al.*, future studies might be warranted to assess whether preoperative optimization and enhanced postoperative surveillance of noncardiac surgical patients with preoperative NT-proBNP greater than 367 pg/ml are associated with improved postoperative outcome. Although not addressed in the meta-analysis of individual patient-level data performed by Potgieter *et al.*, future individual patient-level data meta-analyses could also enhance comparability of studies by leveraging inclusion and exclusion criteria and allowing subgroup analyses and adjustments for covariates.[7]

Potgieter *et al.* assessed NT-proBNP but did *not* assess studies of BNP and its association with 30-day mortality or MI. Although I can anticipate similar shrinkage in OR when compared with previously published aggregate data meta-analyses of BNP in noncardiac surgery, it would also be interesting to see what individual patient-level combined data reveal for assay-specific BNP cut-points for risk prediction in noncardiac surgical patients.

An additional concept that is not addressed in the article by Potgieter *et al.* is that preoperative BNP and NT-proBNP assessments are often reported to have higher specificity but lower sensitivity for predicting adverse postoperative outcomes.[2] What is worth considering for the design of future biomarker studies is that the sensitivity of a biomarker test is likely to be higher if it is assessed for association with an outcome that closely relates to the biology of the biomarker. For example, in a study done by my colleagues and me, the *C*-index was lower for association between preoperative BNP and all-cause mortality up to 5 yr after primary CABG surgery.[8] However, in a later study, we assessed the association between preoperative BNP and heart failure hospitalization or heart failure death during the 5 yr after CABG surgery, and in that study, the *C*-index was higher and equaled 0.75.[3] The biology of BNP makes it unlikely to be highly sensitive for future death from noncardiac causes, but our findings in CABG patients were that assessing a more cardiac-specific outcome improved sensitivity. Ideally, the area under the receiver operating characteristic curve (*C*-index; an indicator of the balance between sensitivity and specificity of a test, with 1.0 indicating a perfect test and 0.75 indicating a good test) would approach 0.75 for the majority of the studies.[9] For more extensive explanation of statistics and biomarker thresholds, Ray *et al.*[9] published a clear and expansive review of statistical evaluation of biomarkers in Anesthesiology. The outcome assessed by Potgieter *et al.* was 30-day postoperative all-cause mortality or nonfatal MI. Many of these outcome events were cardiac, which reinforces the concept that the NT-proBNP cut-point identified in the individual-level meta-analysis by Potgieter *et al.* might be useful for designing future clinical trials of noncardiac surgical patients.

In summary, to move BNP and NT-proBNP assessment into perioperative clinical practice, useful cut-points or risk thresholds must be identified. These cut-points need to demonstrate reasonable sensitivity as well as specificity for adverse postoperative cardiac outcomes. Only then can randomized controlled trials be performed to determine whether better preoperative optimization and closer postoperative surveillance of patients with high BNP result in reduced adverse postoperative cardiac outcomes.[2,3,10,11] Individual patient-level data meta-analysis of studies of cardiac-specific adverse outcomes after surgery may help to identify cut-points in cardiac biomarkers such as BNP, NT-proBNP, and troponins to identify patients at risk who might benefit from further perioperative optimization and intensive care.

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Competing Interests

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