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"I would have everie man write what he knowes and no more."–Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 99, Number 2, August 2007

British Journal of Anaesthesia 151–4 (2007)
doi:10.1093/bja/aem205

Editorial I

Preoperative plasma brain natriuretic peptide concentrations: do they improve our care of high-risk non-cardiac surgical patients?

There is presently much interest in the preoperative identification of high-risk patients undergoing major surgery—with the aim of adopting management strategies which may reduce postoperative morbidity and mortality.[1] In the non-cardiac surgical patient, data for the UK suggest that there may be up to 8000 cardiovascular deaths per year for 5 million surgical procedures performed, with an incidence of 10 times that with regard to morbidity (myocardial infarction, congestive cardiac failure, malignant arrhythmias, and cardiac arrest).[2] The major pathological disorder responsible for these adverse outcomes is ischaemic heart disease, either overt or covert, secondary to atherosclerosis. We, and others, have recently reviewed the role of biomarkers in the identification of at-risk cardiac patients.[3 4]

For a test to be useful as a biomarker, it should to be able to differentiate between the 'healthy' and the 'compromised' patient. In epidemiological terms, it needs to have a high sensitivity (probability that the biomarker will be raised and correctly identify high risk for a complication) and high specificity (such that the biomarker is appropriately low or absent when the risk of complication is absent). For the majority of tests, there is a balance between these two indices; the performance of a test can be further described in terms of a receiver operating characteristic (ROC) curve,[5] which is essentially a graphical plot of sensitivity against 1-specificity, with the inflexion of this curve usually taken as the cut-off value for the diagnostic test. Other commonly used descriptors of the utility of a test or biomarker are the positive and negative predictive values and the relative risk of an adverse event that is provided by a raised concentration of biomarker.

A biomarker that has received a great deal of attention for a number of potential uses is brain (or B-type) natriuretic peptide (BNP). The natriuretic peptides comprise both the atrial and brain (or B-type) natriuretic peptides. In the human, atrial natriuretic peptide (ANP) is primarily produced by atrial myocytes, whereas BNP is produced by both atrial and ventricular myocytes, but primarily by the ventricular ones. BNP was originally identified in extracts of porcine brain. However, in man, it is produced and secreted mainly in the cardiac ventricles. BNP is secreted as the precursor pro-BNP and is cleaved to the active peptide BNP and the inactive N-terminal fragment (NT pro-BNP). The stimulus to release these peptides is myocyte stretch in association with ventricular dilation and pressure overload. The physiological effects of BNP include the augmentation of urinary volume (diuresis), sodium excretion (natriuresis), aldosterone antagonism through inhibition of the renin–angiotensin system, sympathetic autonomic nervous system inhibition, and direct antiproliferative effects on the cardiac myocytes. These effects result in relaxation of vascular smooth muscle and counteraction of hypertrophy and destruction of the myocyte sarcomere structure. Increased plasma concentrations of these peptides have been shown to be associated with hypertension, myocardial hypertrophy, arrhythmias, renal insufficiency, and cerebrally mediated salt wasting.

BNP has shown utility as a diagnostic tool in the evaluation of acute dyspnoea. A blood value <100 pg ml^{-1} was thought to make a diagnosis of congestive cardiac failure unlikely, whereas a value of >500 pg ml^{-1} made it highly likely.[6] BNP has been advocated as a sensitive marker of ventricular dysfunction, with the concentration of BNP varying according to the grade of cardiac failure by the New York Heart Association (NYHA) classification; progressively increasing from Grade I to Grade IV of this scale. Furthermore, the utility of BNP as a biomarker in other settings has been assessed, including screening for preclinical disease in asymptomatic individuals. In elderly subjects (age >80 yr) with no history of cardiac disease, it has been shown that for each increase in the plasma BNP concentration of 50 pg ml^{-1}, there is an associated increase in cardiac events of 1.6-fold and total mortality of 1.4-fold over a 2 yr follow-up period.[7] When the Framingham Offspring Study Database was interrogated,

BNP values >20 pg ml^{-1} were associated with an increase of more than 60% in the long-term risk of death.[8] Other predictive associations were found at lower levels of BNP for heart failure, atrial fibrillation (AF), and stroke. The concentrations of BNP that have shown prognostic use appear lower than the levels commonly used in the setting of heart failure. BNP concentrations have also been used in the risk stratification in patients with clinical congestive cardiac failure, guidance in the selection and titration of therapeutic agents in patients with known disease, and monitoring of response to therapy.

In hypertensive patients, plasma BNP levels independently predict left ventricular mass index, interventricular septal diastolic diameter, and echocardiographic markers of diastolic dysfunction, reflecting the ventricular remodelling process associated with hypertensive heart disease.[9]

Both BNP and NT pro-BNP concentrations have also been shown to have prognostic value in acute coronary syndromes. They can predict outcome after non-ST elevation acute coronary syndrome and predict adverse prognosis in patients presenting with ST-elevation myocardial infarction (STEMI).[10] Even 24 h after STEMI, higher NT pro-BNP concentrations correlate with a larger infarct size and worse outcome.[11] After percutaneous coronary intervention in patients with stable angina, baseline NT pro-BNP measurements have been shown to be a strong independent predictor of death during 1 yr follow-up.[12] An association between BNP and the presence of inducible myocardial ischaemia in patients undergoing exercise stress myocardial perfusion SPECT has also been demonstrated.[13]

Given this level of interest and the versatility of such a biomarker, attention has turned to the surgical setting. Elevated peak postoperative levels of BNP after cardiac surgery have been shown to be associated with a prolonged hospital stay and 1 yr mortality,[14 15] and similarly a preoperative BNP concentration >385 pg ml^{-1} appears to be predictive of postoperative complications and 1 yr mortality.[14] Interestingly, in this study, no correlation was found with aortic cross-clamp time or cardiopulmonary bypass time, unlike other studies which have shown a correlation between postoperative BNP levels and aortic cross-clamp time.[16] BNP concentrations before operation have been shown to be a strong and independent predictor for postoperative AF;[17] however, a different study showed an association between postoperative BNP elevation and postoperative AF, but no association between preoperative raised levels and postoperative AF.[15] Preoperative concentrations of BNP before cardiac surgery are predictive of the need for early inotropic support and prolonged ITU stay,[18] and similarly, preoperative NT pro-BNP levels have been found to be predictive of cardiac failure and the need for inotropic support after coronary artery bypass grafting (CABG) on cardiopulmonary bypass.[19] Elevated concentrations of BNP appear to have a predictive value for complications and 1 yr mortality after cardiac surgery, and in patients exhibiting a severe systemic inflammatory response syndrome after off-pump CABG, there also appears to be significantly higher peak concentrations of NT pro-BNP.[20] The concentrations of BNP and NT pro-BNP seem to peak earlier and return to normal sooner after off-pump CABG when compared with on-pump cardiac surgery.[21] A correlation between cardiac filling pressures measured using a pulmonary artery catheter and BNP concentrations after cardiac surgery has not been demonstrated and plasma BNP concentrations are not predictive of fluid responsiveness in this setting.[16] Even in the setting of cardiac transplantation, NT pro-BNP concentrations have been shown to be elevated from preoperative values 1 week after surgery and a failure of this elevated level to decrease is associated with death.[22]

In critically ill patients, it has been shown that ANP, but not BNP secretion is independent of the underlying disease, suggesting different patho-physiological implications of the different peptides.[23] In patients with severe sepsis who had NT pro-BNP measurements taken on the second day of their diagnosis concentrations >1400 pg ml^{-1} were 3.9 times more likely to die from their sepsis than those with lower values, whereas the concentration of NT pro-ANP was not predictive of death.[24] Similarly, highly elevated concentrations of NT pro-BNP at admission to the intensive care unit (ICU) have been shown to be an independent predictor of mortality,[25] but concentrations of BNP at admission to ITU have not been shown to be predictive of outcome after ICU care.[26]

Interest in BNP as a biomarker after surgery has now extended to the world of non-cardiac surgery. Certainly, as Goldman identified in his risk scoring index in 1977, preoperative left ventricular dysfunction is a strong risk factor for perioperative morbidity and mortality. It therefore seems appropriate that a biomarker of ventricular dysfunction might also predict adverse outcome after non-cardiac surgery. One of the first reports examined the influence of transurethral resection of the prostate on postoperative NT pro-BNP and troponin T concentrations in patients without a prior history of cardiac disease; however, Manikandan and colleagues[27] failed to show any significant postoperative increase in either biomarker or the ECG. In contrast, elevated preoperative N-terminal pro-BNP concentrations were found by both Yeh and colleagues[28] and Feringa and colleagues[29] to be significantly associated with cardiac events after non-cardiac and major vascular surgeries.

In a study of 1590 patients undergoing non-cardiac surgery, Dernellis and Panaretou showed that preoperative elevated concentrations of BNP were an independent biomarker of postoperative cardiac events. BNP levels were a superior predictor to the Goldman multifactorial clinical index, with preoperative BNP concentrations >189 pg ml^{-1} identifying those patients at highest risk.[30] Similarly, a preoperative level >100 pg ml^{-1} has been shown in patients undergoing peripheral vascular surgery with an ASA grade of III or higher to identify those at increased risk of a perioperative fatal or non-fatal myocardial infarction. The

study by Gibson and colleagues[31] first used a cohort of 41 patients to derive the prediction model, which was then tested by a validation cohort of 149 patients. The ROC curve calculated a cut-off value of 108.5 pg ml^{-1} with combined high sensitivity and specificity. Elevation of postoperative BNP concentrations above this value was a significant outcome predictor *even after* adjustment for confounding using multivariate analysis.

In this issue of the *British Journal of Anaesthesia*, Cuthbertson and colleagues[32] report further information on the prediction of perioperative adverse cardiac events in patients undergoing major non-cardiac surgery. They show that raised preoperative BNP levels are seen in patients suffering from perioperative cardiac death or myocardial injury within the first three postoperative days. Their univariate analysis, together with the accompanying ROC curve, suggests a lower cut-off value. In patients with a preoperative BNP of >40 pg ml^{-1}, there was a seven-fold increase in cardiac events in the early postoperative period, as well as a longer hospital stay. There was also an association between the BNP level (expressed in quartiles) and an outcome of either death or troponin I >0.32 ng ml^{-1}. This may imply a 'dose–response' phenomenon associated with elevations of BNP, although this study was neither powered to examine this aspect nor contains enough adverse events to allow us to confirm this as a trend.

So how do the results of Cuthbertson and colleagues compare with those of Gibson and colleagues? Both studies show a significant association between elevated BNP levels and postoperative cardiac outcomes. However, the studies have different cut-off values for BNP, different follow-up periods, and slightly different study populations. Although both studies *in isolation* give a positive association between increased biomarker and outcome, together they offer far greater support to the usefulness of the protein, with an increased combined mortality and morbidity that achieves a difference at the 1% level with a power of 99%!

We therefore concur with the general conclusions of Cuthbertson's paper—'BNP is a useful marker for postoperative outcome; but that larger studies are now needed to confirm the message of these data, and to clarify what (preoperative) BNP levels can add to existing methods of risk stratification'.

Addendum

Since writing this editorial, another study has shown the utility of a single *postoperative* NT pro-BNP determination as a significant biomarker of both in-hospital and long-term cardiac outcomes.[33]

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British Journal of Anaesthesia **99** (**2**): 154–8 (2007)
doi:10.1093/bja/aem204

Editorial II

Vasopressin and its antagonists: what are their roles in acute medical care?

Otherwise known as antidiuretic hormone, vasopressin is a small polypeptide of nine amino acids produced in the hypothalamus and secreted from the posterior pituitary gland. It was first identified more than 100 yr ago as a potent vasopressor. After production of a synthetic analogue in 1954 (for which Vincent Du Vigneaud from Cornell University, USA, received a Nobel Prize),[1] high doses were found to produce coronary artery vasoconstriction. Until recently, vasopressin was largely used only as an antidiuretic agent to treat diabetes insipidus, but it is now being used as a vasopressor in a variety of disease states.

The most important physiological role of endogenous vasopressin is in control of fluid balance. Vasopressin is released when the sensitive osmoreceptors in the hypothalamus detect very small increases in extracellular fluid osmolality (mean threshold value 280 mOsm kg^{-1}).[2] It increases water reabsorption through the collecting ducts of the nephron. In contrast, a much less sensitive trigger for vasopressin release is hypovolaemia—a 10% decrease in arterial volume sensed by baroreceptors in the aortic arch and carotid sinus is needed to stimulate vasopressin release.[2]

Vasopressin acts at three types of vasopressin (V) receptor which all work via G proteins. V_{1a} receptors, found in smooth muscle and the heart, are primarily responsible for the vasoconstrictive properties of vasopressin. V_2 receptors lie within the collecting ducts of the nephron and are involved in water reabsorption. V_{1b} receptors (also known as V_3 receptors), found within the central nervous system, are involved in the secretion of corticotrophin-releasing hormone.