

# Is it Time to Incorporate Natriuretic Peptide Levels into Perioperative Evaluation of Infants with Congenital Heart Disease?

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In this issue of *IMAJ*, Nahum et al. [1] report the measurements of B-type natriuretic peptide in 19 infants undergoing surgery for congenital heart disease. The authors found a preoperative level above 170 pg/ml to be associated with postoperative inotropic support, intensive care unit stay, and length of mechanical ventilation. Similarly, an 8 hour postoperative BNP level  $\geq 1720$  pg/ml was associated with intensive care unit stay. The authors conclude that in infants undergoing heart surgery, preoperative and 8 hour postoperative BNP levels are predictive of inotropic support and longer stay in the ICU.

This is an interesting observation. A potential predictor for perioperative course and complications is of considerable importance. One should, however, be cautious of generalizing the findings of this study as it included a small number of patients with different heart diseases that cause a different hemodynamic burden. Moreover, there are multiple other factors during the operation and the ICU stay that can alter the course of recovery.

The natriuretic peptides are secreted from the heart in response to increased myocardial wall stress due to volume or

pressure overload states [2]. Plasma levels of the natriuretic peptide are elevated in patients with various forms of heart disease. BNP and the amino terminal segment of its prohormone, NT-proBNP, have been studied for more than two decades and are established as biomarkers for specific indications in adult cardiology [3]. Naturally, data in the pediatric age group are far more modest. However, there are substantial data supporting the important role of BNP and NT-proBNP as cardiac biomarkers in infants and children as well [4].

In order to achieve the goal of clinical use, a marker has to fulfill certain essential conditions. These include establishment of age- and gender-dependent reference values, definition of threshold values for various clinical conditions, and, ideally, correlation with disease severity and prognosis. Determination of sensitivity and specificity and predictive values for certain clinical conditions is essential. In addition, the marker levels in many non-cardiac conditions should be determined. Most importantly, a marker should contribute additional information to the available clinical and laboratory evaluation. It should be noted that both BNP and NT-proBNP are measured with different commercial kits. Each kit has different reference values, and not all have established pediatric normal values. We recently learned that not only BNP and NT-proBNP circulate in the blood, but other shorter and longer molecular forms of the peptide are also present. These pep-

tides may be detected as the true peptide and may affect the levels measured by different assays [5]. Peptide levels are higher at an early age. Cantinotti et al. [6] reported the upper limit of BNP levels in healthy infants older than 2 weeks to be 45 pg/ml, significantly lower than the 170 pg/ml in infants with heart disease found by Nahum et al. [1] using the same kit.

The key question of the predictability of the natriuretic peptide levels in preoperative infants and children undergoing cardiac surgery has been studied by others. A number of studies in infants and children have been performed. However, these studies measured different peptides (BNP or NT-proBNP), used different assays, included different age groups and different diseases, and applied different inclusion criteria [7–11]. Some studies excluded patients who died during surgery or less than 6 hours after surgery. Nonetheless, the results of these studies suggest that higher perioperative BNP or NT-proBNP levels are associated with a more difficult ICU course. The heterogeneous nature of these studies precludes determination of the threshold level for predicting worse postoperative outcome.

Cardiac distension, cardiac wall stretch and myocardial injury are known stimuli for BNP and NT-proBNP secretion. However, other factors are associated with elevated natriuretic peptide levels. Peptide levels are high soon after birth and decrease thereafter [4]. Children with febrile illness and patients with sepsis have elevated BNP/NT-proBNP levels even with normal cardiac function [12]. This is probably due to the activa-

BNP = B-type natriuretic peptide  
ICU = intensive care unit

NT-proBNP = N-terminal prohormone of brain natriuretic peptide

tion of stress mediators, acidosis, renal impairment or a combination of these factors. Theoretically, it is possible that the patients with higher preoperative BNP or NT-proBNP levels are less likely to be hemodynamically compensated and have an activated stress system. These patients are more likely to have a difficult postoperative course. Interestingly, but not surprisingly, BNP levels did not correlate with shortening fraction, an echocardiographic measure of contractility. Shortening fraction is known to be of limited prognostic value in adults with heart failure [13].

A comprehensive evaluation of operative risk was performed in the large RACHS-1 study, a system for predicting in-hospital mortality after surgery for congenital heart disease among children under the age of 18 years. This multicenter study included 4602 surgeries. The predicting factors that emerged were the type of surgery, age (less than 1 year), prematurity, major non-structural anomalies, and combination procedures [14]. The mortality ranged from 0.4% in the lowest category to 47.7% in the highest. Could the addition of preoperative age-adjusted BNP to the RACHS-1 model differentiate patients with the same disease and other risk factors to higher and lower risk subgroups? The answer is probably yes, but this should be scientifically established. Studies on the

perioperative BNP/NT-proBNP levels are small and correlate peptide levels with postoperative course and not with mortality.

Should high preoperative BNP or NT-proBNP levels be a warning sign for a rough postoperative course? Should patients with high BNP be stabilized with inotropic support or diuretics to reduce BNP before undergoing surgery? It seems too early for such conclusions. The available limited data, however, support the statement that a high peptide level should alert the physician to a potential difficult postoperative course.

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## Capsule

### T helper-1 cell cytokines drive cancer into senescence

Cancer control by adaptive immunity involves a number of defined death and clearance mechanisms. However, efficient inhibition of exponential cancer growth by T cells and interferon- $\gamma$  (IFN $\gamma$ ) requires additional undefined mechanisms that arrest cancer cell proliferation. Braumüller et al. show that the combined action of the T helper-1 cell cytokines IFN $\gamma$  and tumor necrosis factor (TNF) directly induces permanent growth arrest in cancers. To safely separate senescence induced by tumor immunity from oncogene-induced senescence, the authors used a mouse model in which the Simian virus 40 large T antigen (Tag) expressed under the control of the rat insulin promoter creates tumors by attenuating p53- and Rb-mediated cell cycle control. When combined, IFN $\gamma$  and TNF drive Tag-expressing cancers into senescence by

inducing permanent growth arrest in G1/G0, activation of p16INK4a (also known as CDKN2A), and downstream Rb hypophosphorylation at serine 795. This cytokine-induced senescence strictly requires STAT1 and TNFR1 (also known as TNFRSF1A) signaling in addition to p16INK4a. In vivo, Tag-specific T helper-1 cells permanently arrest Tag-expressing cancers by inducing IFN $\gamma$  and TNFR1-dependent senescence. Conversely, Tnfr1 $^{-/-}$  Tag-expressing cancers resist cytokine-induced senescence and grow aggressively, even in TNFR1-expressing hosts. Finally, as IFN $\gamma$  and TNF induce senescence in numerous murine and human cancers, this may be a general mechanism for arresting cancer progression.

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