# Pre and Post-extubation B-type Natriuretic Peptide Values in Postoperative Congenital Heart Disease

**OBJECTIVE** To determine whether pre and post extubation B-type natriuretic peptide values can predict extubation failure within 48 hours in post-operative congenital heart disease.

**HYPOTHESIS** An increased value in post-extubation BNP value can predict extubation failure and need for reintubation within 48 hours in neonates ≤ 30 days of age following cardiac surgery with RACHS-1 score of ≥3.

**BACKGROUND AND SIGNIFICANCE**

B-type natriuretic peptide (BNP) is a polypeptide cardiac hormone that is secreted by cardiac myocytes. BNP is predominantly released from the ventricles in response to increased ventricular pressure and volume load. The release of BNP during cardiac stress results in inhibition of renin and aldosterone secretion thereby allowing for natiuresis with a decrease in afterload, preload, and reduced ventricular end-diastolic pressure. This results in increased cardiac output and improved diastolic function [1].

BNP in Congenital Heart Disease

BNP has become an important biomarker in heart failure. In adults, BNP values are used to differentiate heart disease from lung disease, to assess perioperative cardiovascular risk factors, and to predict outcomes and guide therapy in individuals with heart failure. However, little is known with regards to its clinical implications in the setting of pediatric congenital heart disease (CHD)[2-8].

Law et al sought to describe the accuracy of BNP to diagnose significant cardiovascular disease in children. Subjects (N=100) without known heart disease who presented with findings concerning for an underlying heart condition were evaluated with serum BNP levels at time of cardiology consultation. Subjects were divided into a neonatal (N= 42, 0-7 days) and older age group (N= 58, >7days -19 years). In neonates who were found to have cardiovascular disease, the median BNP value was 526pg/ml vs 96 pg/ml (p <0.001) in those without disease. In older children, the median BNP was 122pg/ml in those with disease compared to median of 22 pg/ml in those without disease (p <0.001). Higher BNP values were found in subjects with disease related to an anatomic defect, those who had longer hospitalization, or those who died. This study concluded BNP is a reliable test to diagnose significant structural or functional cardiovascular disease in children and found that optimal cutoffs differed from adult values [9].

In a blinded, observational case series, Niedner and colleagues, characterized BNP values and delineated distinguishable patterns among subgroups of children (N=105) undergoing surgical repair of congenital heart disease. Patients were subgrouped as neonatal and non-neonatal. The median 24 hour postoperative BNP value for neonates was 1506 (782-3784) pg/mL vs. 286 (169-578) pg/mL for non-neonates (p< 0.001). Postoperative BNP values correlated with inotropic requirements, duration of open chests, need for ventilation, intensive care length of stay, and duration of hospitalization. In addition, children undergoing Fontan palliations were found to have lower postoperative BNP (median 150 vs 306 pg/mL, p<0.001) with a three-fold higher incidence of low cardiac output syndrome (LCOS) and longer length of hospitalization when compared to children undergoing biventricular repairs. BNP typically peaked 6-12 hours postoperatively with an earlier peak and higher magnitude of rise noted in neonates. The authors concluded perioperative BNP correlates with severity of illness and duration of therapies in CHD, however a wide variation of BNP values within and between CHD lesions makes an isolated BNP value difficult to apply clinically [10].

Berry et al studied the prognostic value of BNP in the postoperative care of children ungergoing palliation of single-ventricle congenital heart disease (n=23). This study specifically evaluated children undergoing Norwood (n=13), bidirectional cavopulmonary anastomosis (BCPA) (n=5), or Fontan (n=5) operation. This study found BNP levels were significantly higher in patients following the Norwood procedure compared to a BCPA or Fontan procedure. Postoperative BNP values at 6 and 12 hours correlated significantly with duration of inotropic support and length of hospitalization. An increase in BNP values within 48 hours following extubation was noted in 92% of patients undergoing Norwood procedure and concluded this may be reflective of the degree of underlying cardiopulmonary instability [11].

Shih and colleagues described perioperative patterns of BNP values of infants and children (n=49, ages 1day to 15 years) undergoing cardiopulmonary bypass for repair of congenital heart disease. BNP levels increased after cardiopulmonary bypass with an 8-fold peak increase at 12 hours (P <0.005). Postoperative BNP values were associated with duration of mechanical ventilation and presence of low cardiac output syndrome. A postoperative BNP value greater than 540 pg/mL predicted mechanical ventilation for more than 48 hours with a sensitivity of 88.9% and specificity of 82.5%. Postoperative BNP values greater than 815 pg/mL also predicted the presence of low cardiac output syndrome within 48 hours of surgery with a sensitivity of 87.5% and specificity of 90.2%. This paper concluded BNP values may be a useful tool in the postoperative management of patients undergoing repair of congenital heart disease [12].

BNP as a Predictor of Successful Weaning from Mechanical Ventilation

Mechanical ventilation can play a significant role in cardiopulmonary interactions and, in patients with cardiovascular dysfunction, it is often difficult to assess the effects of positive pressure ventilation. In adults, BNP has been evaluated as a potential predictor of extubation success. Chien et al. used changes in BNP values to predict weaning success during spontaneous breathing trials in adults. Patients with respiratory failure were evaluated with BNP values at the beginning of and 2 hours after a spontaneous breathing trial (SBT). All patients who successfully completed the spontaneous breathing trial were extubated. There was no difference in baseline BNP values, however, patients who were reintubated within 48 hours had significantly greater increases in BNP at the end of the SBT compared to the extubation success group. An increase in BNP by >20% during the SBT was found to have the best sensitivity (91%), specificity (88%), positive and negative predictive values (97% and 70%, respectively) by ROC curves. Combining the change in BNP value with the SBT for use as extubation criteria increased extubation success rate to 95% from 78% compared with using the SBT alone. This paper concluded measuring BNP levels during a spontaneous breathing trial may improve the predictive value of SBT on the weaning outcome [13].

In the setting of complex congenital heart disease, mechanical ventilation has an exaggerated impact on cardiopulmonary interactions. It is often difficult to determine when the post-operative patient is ready for extubation using a ventilator weaning protocol alone. The paper published by Neider and colleagues characterizing perioperative patterns of BNP in congenital heart disease commented that BNP levels transiently increased following extubation, but did not report nor describe this data in depth [10]. Berry et al noted an increase in BNP values following extubation in 92% of patients undergoing Norwood surgical procedure. They postulated this may be indicative of the degree of underlying cardiopulmonary instability [11]. We postulate that the use of serial BNP values in such patients may aid in determining the appropriate time for extubation and guide the practitioner in adjusting peri-extubation inotropic support.

**RESEARCH DESIGN AND METHODS**

STUDY DESIGN**:** Prospective, observational, blinded pilot study.

HYPOTHESIS: An increased value in post-extubation BNP value can predict extubation failure and need for reintubation within 48 hours neonates ≤ 30 days of age following cardiac surgery with RACHS-1 score of ≥3.

PRIMARY OUTCOME VARIABLE: A 20% change in pre and 2 hour post-extubation BNP value.

SECONDARY OUTCOME VARIABLES: A 20% change in BNP values at 6 and 12 hours post-extubation.

INCLUSION CRITERIA:

1. Neonates ≤ 30 days of age with congenital heart disease and RACHS-1 score ≥3 admitted to the CMH PICU postoperative

2. Need for full mechanical ventilatory support at time of post-operative admission

3. Informed consent from parents(s)/legal guardian

EXCLUSION CRITERIA:

1. Infants who have already began weaning of the ventilator

2. Recent use of immunotherapy using monoclonal antibodies or concurrent nesiritide infusion

3. Lack of informed consent

RATIONALE FOR RACHS-1 SCORING SYSTEM

The risk adjustment for in-hospital mortality among children younger than 18 years after surgery for congenital heart disease (RACHS-1) was created by an 11-member national group of pediatric cardiologists and cardiac surgeons [Appendix 1]. Their expert clinical judgment was used to place surgical procedures for congenital heart disease into 6 risk categories after reviewing 4602 surgical patients in the Pediatric Cardiac Care Consortium and 4493 patients from three statewide hospital discharge data sets. Mortality rates were 0.4% in category 1, 3.8% in 2, 8.5% in 3, 19.4% in 4, and 47.7% in 6. There was insufficient number of cases in category 5 to calculate mortality [14]. This is the first method of risk adjustment for short-term mortality in congenital heart disease surgery that has incorporated the anatomic diversity seen in such surgical procedures. This allows for meaningful comparisons across groups of patients, and helps to identify high risk groups, such as the population being evaluated in this study.

SUMMARY OF VENTILATORY WEANING PROTOCOL

Once the patient is breathing spontaneously and is ready for ventilator weaning as deemed by the attending physician, the ventilator mode will be switched to pressure regulated volume-controlled, pressure-controlled, or volume-controlled, synchronized, intermittent, mandatory ventilation. The respiratory rate will be weaned according to the Children's Mercy Hospital ventilator weaning protocol. Goal oxygen saturation will be determined by the attending physician according to the patient's underlying cardiac physiology. Criteria for extubation will include FiO2 of ≤ 0.4 with maintenance of goal arterial oxygen saturation, a respiratory rate within 20-60 breaths per minute, and exhaled tidal volume ≥5ml/kg on a positive end expiratory pressure of ≤5 cm $H_2O$, and pressure support of ≤10 cm $H_2O$ for a minimum of one hour. The attending physician will approve all planned extubations.

MEASUREMENTS:

Blood will be drawn via indwelling arterial line (or central venous line if arterial line not available) prior to the start of ventilator weaning in a synchronized, intermittent, mandatory ventilator mode , following one hour of pressure support trial, and at 2, 6, and 12 hours following extubation. If the patient undergoes more than one pressure support trial, a BNP value will only be obtained once and only during the first pressure support trial that lasts at least 1 hour. If the patient is reintubated prior to the end of the study period, a BNP value will be drawn as soon as clinically appropriate at the time of re-intubation. Total blood loss 2.5ml (0.5ml per BNP test) will be required for the testing.

Additional data collection (to be obtained from the electronic medical record and the HeartCenter Database) will include:

1. Demographics: Age, weight, diagnosis, surgical procedure

2. Clinical data: length of mechanical ventilation, need and reason for reintubation, use of non-invasive ventilator support following extubation, echocardiogram results before and after extubation if performed, inotropic support scores, NIRS values before and after extubation, length of ICU stay

3. Laboratory data: any additional BNP values obtained (unrelated to study), arterial and venous blood gas values before and after extubation (if obtained)

**RISKS TO SUBJECTS**

SOURCES OF MATERIAL: Blood specimens will be obtained from indwelling catheters that have been routinely placed for perioperative care. The patient will be weaned from the ventilator and extubated using the ventilator weaning protocol discussed above. Data will be collected from the inpatient written and electronic chart along with data retrieved via the Heart Center Database (IRB # 03 06-067E) located within The Ward Family Center for Congenital Heart Disease.

POTENTIAL RISKS: A small risk of hemodynamic instability (tachycardia, hypotension) due to blood draws exists in small infants with myocardial depression after cardiopulmonary bypass and/or heart surgery. There is also a small risk of anemia related to blood draws which could result in the need for a blood transfusion. Blood draws will be limited to the smallest amount necessary for the proposed lab tests. A total of 0.5ml is needed for each BNP lab test, and each child will potentially require a total of 2.5ml blood sampling during the study period. Should the ICU physician deem that blood draws are unsafe in any patient, blood will not be obtained.

**FINANCIAL CONSIDERATIONS AND FUNDING**

Each BNP lab test costs $118 at the research price and includes the cost of specimen collection and courier fees. Each study participant will require up to $590 to complete the study.

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