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B-Type Natriuretic Peptide (BNP) in Neonates, Infants and Children Undergoing Cardiac Surgery

Peter E. Oishi[1,2], Aida Field-Ridley[3], Sanjeev A. Datar[1] and Jeffrey R. Fineman[1,2]
[1]*University of California San Francisco, Pediatrics, Critical Care Medicine,*
[2]*Cardiovascular Research Institute, University of California San Francisco,*
[3]*Department of Pediatrics,University of California, Davis, Pediatrics, Critical Care Medicine,*
USA

1. Introduction

In 1988 Sudoh and colleagues described a novel natriuretic peptide in porcine brain -- brain natriuretic peptide(Sudoh et al. 1988). In fact, the peptide is most abundant in the heart and thus it is now commonly termed B-type natriuretic peptide (BNP). Myocyte pressure and/or stretch results in the release of BNP, and BNP levels are easily quantified by several commercially available assays. Data from numerous studies have now firmly established a role for BNP as a biomarker for diagnosis, prognostication, and management of adults with cardiac disease, including those undergoing cardiac surgery(Silver et al. 2004; Mitchell and Webb 2011; Rodseth, Padayachee, and Biccard 2008; Fellahi et al. 2011). Unfortunately, far fewer data are available on the role of BNP in the management of neonates, infants, and children who require cardiac surgery. This chapter will provide a brief review of these data in order to understand the potential utility of BNP determinations in this population.

2. Natriuretic hormone system

Beginning with the observation by de Bold and colleagues that rats infused with atrial tissue extracts developed natriuresis and diuresis, much has been learned over the past three decades about the role of the natriuretic hormone system in the homeostatic control of fluid balance and vascular tone(de Bold et al. 1981). The natriuretic hormone system comprises several related peptides that activate specific receptors, particularly in the kidneys, myocardium, and vasculature, which use cyclic guanosine 3',5'-monophosphate (cGMP) as a second messenger(Levin, Gardner, and Samson 1998). These peptides include atrial natriuretic peptide (ANP), BNP, C-type natriuretic peptide (CNP), dendroaspis natriuretic peptide (DNP), kaliuretic peptide, and urodilantin. The primary stimulus for their release is an increase in intravascular or cardiac volume, that causes increased atrial stretch, ventricular wall stress, vascular shear stress, intravascular volume, and/or intravascular sodium concentration(Levin, Gardner, and Samson 1998). The precise roles of individual natriuretic peptides depend upon their distribution and abundance within the cardiovascular system, as well as the specific stimulus for their release(Levin, Gardner, and Samson 1998).

3. B-Type natriuretic peptide (BNP)

BNP is predominantly produced in the cardiac ventricles. However under pathologic conditions, such as fluid overload, the cardiac atrium can also become a significant source of BNP(Sudoh et al. 1988; McGrath, de Bold, and de Bold 2005). Biosynthesis of BNP begins with a 134 amino acid precursor, preproBNP. Stimuli, such as myocyte stretch, trigger the cleavage of preproBNP forming proBNP, which is subsequently cleaved by a serine protease to the active C-terminal 32 amino acid hormone, BNP, and the inactive N-terminal proBNP (NT-proBNP). BNP binds to 3 known cell membrane receptors, termed natriuretic peptide receptors (NPR-A, NPR-B, and NPR-C). NPR-A and NPR-B are transmembrane receptors that activate particulate guanylate cyclase, which catalyzes the conversion of guanosine triphosphate to cGMP. The third receptor, NPR-C, is involved in clearance via endocytosis. Circulating BNP is also inactivated by cleavage by neutral endopeptidases found in vascular cells and renal tubules (Figure 1) (Yandle 1994; Silver et al. 2004). Animal studies suggest that approximately half of natriuretic peptide clearance is via the NPR-C receptor and half via endopeptidase degradation, but the relative contributions in the human are unclear.

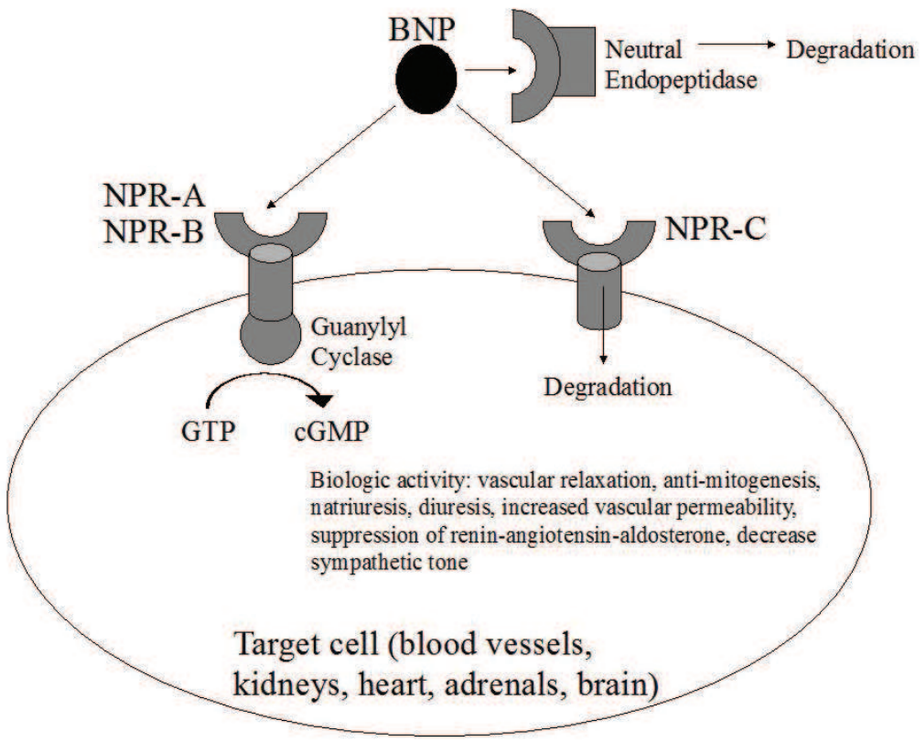


Fig. 1. A schematic of B-type natriuretic peptide (BNP) signaling. BNP binds to 3 natriuretic peptide receptors (NPR), types A, B, and C, on various target cells located in the vasculature, kidney, heart, adrenal glands, and brain. NPR-A and NPR-B are high-affinity receptors with an extracellular binding domain, a single membrane-spanning region, and an intracellular guanylylcyclase domain. Guanylylcyclase catalyzes the conversion of guanosine-5'-triphosphate (GTP) to guanosine-3',5'-cyclic monophosphate (cGMP). BNP is degraded by two mechanisms. Neutral endopeptidases degrade circulating BNP, and binding to NPR-C results in receptor internalization and degradation by endocytosis. NPR-C is then recycled to the cell membrance (not shown).

The mechanisms that mediate BNP release and metabolism in health and disease are incompletely understood. In addition, the effect of development on these mechanisms is unknown, but clearly may have great relevance in a pediatric population. Active BNP is stored in the atria in specific storage organelles(McGrath, de Bold, and de Bold 2005). Basal BNP levels result from continuous secretion from the atria. With acute myocardial distention, BNP release increases from this storage pool, in a manner independent of BNP synthesis. However, under acute, sub-acute and chronic conditions of increased cardiac volume or pressure loading, increases in circulating BNP are maintained due to ventricular re-expression of the fetal gene program (Zhang, Carreras, and de Bold 2003; Hama et al. 1995). In addition to volume and pressure loading, acute myocardial ischemia, α agonist stimulation, endothelin-1, and inflammatory mediators, such as tumor necrosis factor-α and interleukin-1β, result in rapid ventricular expression of BNP(Hama et al. 1995). The primary actions of BNP are vascular smooth muscle relaxation and anti-mitogenesis, mediated by cGMP, diuresis, caused by a shift of intravascular volume into the interstitium, and natriuresis, caused by antagonism of renin and aldosterone release(McGrath, de Bold, and de Bold 2005; Sudoh et al. 1988; Yandle 1994).

Of all the natriuretic peptides, BNP has emerged as the most useful biomarker for cardiac disease. Its major advantage over the other natriuretic peptides is the fact that it is produced predominantly in the ventricles, as opposed to the atrium (ANP) or the vascular endothelium (CNP)(Silver et al. 2004; Costello, Goodman, and Green 2006). Both active BNP and the inactive byproduct of its production, NT-proBNP, are used as biomarkers. BNP levels may be better suited to follow dynamic alterations in myocardial performance given the shorter circulating half-life of BNP compared to NT-proBNP (20 minutes vs. 60-120 minutes)(Costello, Goodman, and Green 2006). In addition, the kidneys excrete NT-proBNP, and thus renal function, independent of myocardial function, has a greater influence on NT-proBNP levels than BNP levels.

Limited data suggest that BNP levels are high at birth but fall during the first week of life, reaching levels below adult values by 2 weeks of age. Interestingly, although levels in boys tend to decrease with age, girls have an elevation during the second decade of life that is associated with puberty (Koch and Singer 2003; Yoshibayashi et al. 1995; Ationu and Carter 1993).

4. BNP in pediatric heart disease

In comparison to the adult experience, there are far fewer data regarding BNP in pediatric cardiac disease(Das 2010). Knirsch and colleagues measured BNP levels before and during treatment in 522 pediatric patients (age of 6.4±5.2 years, range of 14 days to 18 years) with congenital heart disease, cardiomyopathies, or pulmonary arterial hypertension(Knirsch et al. 2011). They found that BNP levels were elevated in each type of heart disease, and that levels fell in all groups with therapy.

As opposed to adults with congestive heart failure, BNP levels in infants and children with congenital heart disease are quite varied, and are dependent in part upon the age of the patient and the specific physiology associated with the cardiac defect. For example, Law and colleagues performed a study that included 42 neonates and 58 older children between the age of 7 days and 19 years presenting in an acute care setting with symptoms potentially attributable to heart disease. BNP levels were higher in both age groups in those patients with heart disease compared to those without heart disease, but the cut-off values differed. A BNP level of 170 pg/ml was 94% sensitive and 73% specific for heart disease in neonates,

whereas a lower level of 41 pg/ml was 87% sensitive and 70% specific for heart disease in the older patients(Law et al. 2009). Koch and colleagues found in a study of 288 pediatric patients (mean age of 6 years) with congenital cardiac defects that normal BNP levels did not exclude cardiac pathology such as the presence of structural defects or ventricular hypertrophy, but rather were associated with the extent of ventricular impairment(Koch, Zink, and Singer 2006). Conversely, Cantinotti and colleagues studied 152 neonates with congenital heart disease and 154 healthy neonatal controls, and found the BNP levels were higher in neonates with congenital heart disease than controls with a diagnostic accuracy defined by the area under the curve (on receiver operating characteristic analysis) of 0.935 for neonates with congenital heart disease between 4 and 30 days of age(Cantinotti et al. 2010). Thus, it appears that age modifies the diagnostic utility of BNP for cardiac disease in pediatric patients. In fact, in a separate study Koch and colleagues demonstrated age-dependent differences in the metabolic clearance of BNP and NT-proBNP(Koch, Rauh, et al. 2006).

A number of studies indicate that cardiopulmonary hemodynamics also modify the diagnostic utility of BNP in pediatric patients with congenital heart disease. For example, in a study of infants and children with ventricular septal defects, Suda and colleagues found that BNP levels correlated with the pulmonary-to-systemic blood flow (Qp:Qs) ratio and the mean pulmonary arterial pressure(Suda, Matsumura, and Matsumoto 2003). Koch and colleagues demonstrated similar correlations, in their study of 288 patients with various cardiac defects(Koch, Zink, and Singer 2006). They found that in patients with left-to-right shunts, BNP levels were increased and correlated with shunt volume, systolic right ventricular pressure, mean pulmonary artery pressure, and pulmonary vascular resistance(Koch, Zink, and Singer 2006). Likewise, Kunii and colleagues compared BNP levels between normal children (n=253), and children with ventricular septal defects (n=91), patent ductus arteriosus (n=29), and atrial septal defects (n=34). Like the studies of Suda and Koch, they found that BNP levels correlated with the Qp:Qs ratio, and also the left ventricular end-diastolic volume, and the right ventricular to left ventricular pressure ratio(Kunii et al. 2003). Mainwaring and colleagues also found a positive correlation between preoperative BNP levels and the Qp:Qs ratio in a study of 18 patients (2 months – 15.6 years of age) with ventricular septal defects(Mainwaring et al. 2007). Ozhan and colleagues found the same relationship between BNP and the Qp:Qs ratio in their study of 35 children (mean age 70±129 weeks) with ventricular or atrial septal defects. Receiver operating characteristic analysis found that a plasma BNP cutoff of ≥20 pg/ml was 69% sensitive and 79% specific for a Qp:Qs of greater than 1.5(Ozhan et al. 2007).

A number of studies of premature neonates found that BNP levels correlated with the degree of shunting across a patent ductus arteriosus and predicted hemodynamic significance as determined by echocardiography-based criteria(Choi et al. 2005; Flynn et al. 2005; Puddy et al. 2002; Sanjeev et al. 2005; Holmstrom and Omland 2002; da Graca et al. 2006). However, the precise cut-off value for BNP that was predictive varied widely. For example, Choi and colleagues reported that a BNP level of > 1110 pg/ml was 100% sensitive and 95% specific for the presence of a hemodynamically significant patent ductus arteriosus, while Sanjeev and colleagues reported a 92% sensitivity with a cut-off level of 70 pg/ml(Choi et al. 2005; Sanjeev et al. 2005).

Holmgren and colleagues studied 38 patients with single ventricular physiology. They found that BNP levels were higher in patients after first stage palliation (31.6 pg/ml) compared to patients after second and third stage palliation (6.7 and 9 pg/ml, respectively). In fact, BNP levels in patients after second and third stage palliation did not differ from

normal control patients, but interestingly, BNP levels were higher in those patients with single ventricles of right ventricular morphology compared to left ventricular morphology(Holmgren et al. 2008). In contrast, Koch and colleagues studied 48 patients with d-transposition of the great arteries, after arterial switch procedure, or congenitally corrected transposition of the great arteries. They found no difference in BNP levels between patients with systemic ventricles of right ventricular morphology compared to left ventricular morphology(Koch, Zink, and Singer 2008). They did, however, find correlations between BNP and the severity of tricuspid regurgitation and decreasing exercise capacity. Likewise, Inuzuka and colleagues measured BNP levels in 51 patients (mean age 1.1 years) with single ventricular defects undergoing cardiac catheterization before second stage palliation. Mean BNP levels were 90.4 pg/ml. BNP levels above 100 pg/ml were associated with increased Qp:Qs, end-diastolic volume, AV valve regurgitation, and lower ventricular mass to end-diastolic volume ratio, all consistent with an inadequate adaptation to volume overload(Inuzuka et al. 2011). In addition, multivariate regression analysis demonstrated that the BNP concentration was independently predictive of death or the need for cardiac transplantation (with a hazard ratioof 3.05, CI: 1.06-8.83)(Inuzuka et al. 2011).

Thus, it is clear that BNP determinations can provide physiologically relevant information about individual patients, but that finding cut-off values that can be generalized for clinical use across the spectrum of congenital heart disease may not be possible. Indeed, in adult patients the primary utility of BNP determinations is in establishing the diagnosis of congestive heart failure in acute care settings(Maisel et al. 2002). In a pediatric population, the questions are more diverse. They might include, when to repair a left-to-right shunt, when to proceed with staged palliation of single ventricle defects, or when to refer for cardiac transplantation. However, even studies focused on pediatric heart failure have revealed a wide range of BNP values, again likely related at least in part to age and cardiopulmonary hemodynamics. For example, in a study of infants and children with biventricular hearts and chronic left ventricular dysfunction, Price and colleagues found that a BNP level of ≥300 pg/ml was predictive of death, hospitalization, or listing for cardiac transplant(Price et al. 2006). Shah and colleagues also found that increasing BNP was associated with heart failure in their study of 29 patients with single ventricular physiology, but with a ten-fold lower cut-off of 30 pg/ml (Shah, et al., 2009).

5. BNP as a biomarker following cardiac surgery

5.1 Early post-operative period

As a cardiac hormone with a relatively short circulating half life that is dynamically released in response to deranged myocardial performance, BNP appears perfectly suited for the perioperative management of pediatric patients undergoing cardiac surgery for repair or palliation of congenital cardiac defects.

A number of investigators have studied perioperative BNP levels in neonates, infants, and children undergoing cardiac surgery. Ationu and colleagues measured perioperative BNP levels in 9 children undergoing repair of congenital heart defects(Ationu et al. 1993). In that study, BNP levels decreased at 12 hours following surgery(Ationu et al. 1993). Most studies, however, have found increases in BNP and NT-proBNP levels after surgery. Costello and colleagues measured natriuretic peptide levels, including BNP, in 5 infants undergoing surgical repair of left-to-right shunts(Costello et al. 2004). As opposed to ANP and DNP, BNP concentrations increased after cardiopulmonary bypass. Sun and colleagues measured BNP levels before and after surgery in 27 infants and children undergoing biventricular

repair and 27 patients undergoing palliation of univentricular congenital heart defects(Sun et al. 2005). Plasma BNP levels increased after bypass in patients with biventricular defects, but not in patients with univentricular defects(Sun et al. 2005). Costello and colleagues examined BNP levels before and following cardiac surgery in 25 infants and children with congenital heart disease undergoing complete or palliative repair with the use of cardiopulmonary bypass(Costello et al. 2004). BNP levels increased postoperatively, and remained elevated over the first postoperative day. The increase in BNP from baseline to 12 hours was associated with the cardiopulmonary bypass time.Koch and colleagues measured BNP levels in 65 pediatric patients (age 4 days – 17 years, mean age of 3.6), undergoing surgical repair of congenital cardiac defects preoperatively, and for one week after surgery(Koch, Kitzsteiner, et al. 2006). BNP levels increased after surgery (from a median of 31 pg/ml to 453 pg/ml) and remained elevated over the first week, with a bimodal pattern (initial peak at 1.3 days and a second peak at 5.1 days after surgery). Postoperative BNP levels correlated with cardiopulmonary bypass time and serum lactate concentrations on the first postoperative day.

Shih and colleagues conducted the first study demonstrating that BNP predicted outcome after cardiac surgery in children(Shih et al. 2006). BNP levels were determined before and after surgery in 51 patients. They found that BNP levels increased after surgery, peaking at 12 hours, and that BNP levels 12 hours following surgery were predictive of a requirement for mechanical ventilation beyond 48 hours and the presence of low cardiac output syndrome within the first 48 hours, postoperatively. Further, the study found that 12-hour BNP levels of 540 pg/ml had a sensitivity of 88.9% and a specificity of 82.5% for predicting the need for mechanical ventilation beyond 48 hours, and that a 12-hour BNP of 815 pg/ml had a sensitivity of 87.5% and a specificity of 90.2% for predicting the development of low cardiac output syndrome.

Similarly, Perez-Piaya and colleagues measured NT-proBNP levels in 68 patients (0-15 years of age) undergoing cardiac surgery(Perez-Piaya et al. 2011). They found that NT-proBNP levels increased postoperatively, peaking at 24 hours. Moreover, peak NT-proBNP levels correlated with risk adjustment congenital heart surgery-1 scores, length of cardiopulmonary bypass, inotropic score, duration of mechanical ventilation, and intensive care unit length of stay. In addition, preoperative NT-proBNP levels were independent predictors of intensive care unit length of stay. Gessler and colleagues also measured NT-proBNP levels before and after cardiac surgery in 40 children(Gessler et al. 2006). In their study, higher preoperative levels were noted in patients with a complicated postoperative course.

It is well known that neonates undergoing cardiac surgery and patients with single ventricular physiology represent high-risk groups. Hsu and colleagues examined BNP levels before and after surgery in 31 consecutive neonates undergoing repair or palliation of their cardiac defects(Hsu et al. 2007). BNP levels at all time points were markedly elevated, compared to published normal values. But interestingly, as opposed to the majority of studies of older patients, they found that 24-hour postoperative BNP levels were lower than preoperative BNP levels in most patients (75%). However, in those patients whose BNP levels increased after surgery outcomes were worse. In fact, an increase in post-operative BNP was associated with an increased incidence of low cardiac output syndrome (100% vs. 36 %), and fewer ventilator-free days (17 ± 13 days vs. 25 ± 3 days), and predicted the 6-month composite endpoint of death, an unplanned operation, or cardiac transplant (57% vs. 0%). Furthermore, an increase in BNP after surgery had a sensitivity of 100% and a specificity of 87% for predicting a poor postoperative outcome. Notably, neither arterial-

venous oxygen saturation differences ($AVdO_2$) nor lactate levels (or their corresponding changes) were associated with postoperative outcomes in this study(Hsu et al. 2007).
In another neonatal study, Cannesson and colleagues measured perioperative BNP levels in 30 neonates undergoing the arterial switch operation (ASO) for d-transposition of the great arteries(Cannesson et al. 2007). Contrary to the findings of Hsu, BNP levels increased over the first 48 hours postoperatively. However, like the study by Hsu these investigators found that postoperative BNP levels predicted adverse clinical outcomes, including prolonged mechanical ventilation, prolonged stay in the intensive care unit, low cardiac output syndrome, and the need for inotropic support. These investigators found that a BNP level of >160 pg/ml, 6 hours postoperatively, predicted a complicated postoperative course with a sensitivity of 93% and a specificity of 67%. Similarly, Niedner and colleagues studied 102 neonates and non-neonatal controls undergoing surgical repair for various congenital cardiac defects(Niedner et al. 2010). They found that BNP levels increased after surgery, peaking at 12 hours. Levels at 24 hours were significantly higher in neonates than in non-neonates (median of 1506 vs 286 pg/ml). In addition, postoperative BNP levels correlated with the inotropic requirement, duration of mechanical ventilation, and intensive care unit and hospital length of stay. When comparing the various cardiac defects, these investigators found great variability between lesions and noted the significant impact of age, with postoperative elevations occurring earlier and to a much greater magnitude in neonates compared to older children. One might speculate that the differences between the neonatal studies of Hsu, Cannesson, and Niedner relate in part to differences between single and bi-ventricular physiology, and the impact of surgery on ventricular volume and pressure loading. Furthermore, these studies demonstrate that the potential clinical utility for BNP determinations as a part of management after cardiac surgery may depend upon analyzing patterns of change, as opposed to single time points. Moreover, relevant patterns of change may differ between cardiac defects and age groups.
In fact, Berry and colleagues studied 20 neonates, infants, and children undergoing various stages of palliation for cardiac defects with single ventricle physiology(Berry et al. 2007). They found that BNP levels were highest in neonates undergoing a Norwood procedure compared with patients undergoing bidirectional cavopulmonary anastomosis or a Fontan procedure. They also found that postoperative BNP levels were predictive of hospital length of stay and postoperative inotropic support.Likewise, Hsu and colleagues measured perioperative BNP levels in 36 infants and children undergoing bidirectional cavopulmonary anastomosis (n=25) or total cavopulmonary connection (n=11)(Hsu et al. 2008). Plasma BNP levels were measured before and at various time points after surgery. They found that BNP levels increased after surgery, peaking at 12 hours in most patients. In the bidirectional cavopulmonary anastomosis group, patients with a 12-hour BNP level of ≥500 pg/mL had a longer duration of mechanical ventilation, intensive care unit stay, and hospital stay. A 12-hour BNP level of ≥500 pg/mL had a sensitivity of 80% and a specificity of 80% for predicting an unplanned surgical or transcatheter cardiac intervention, including transplantation. In the total cavopulmonary connection group, preoperative BNP levels were highest in patients with total cavopulmonary connection failure compared with patients with a good outcome, whereas postoperative BNP levels were not predictive of outcome.Importantly, preoperative cardiac catheterization data did not correlate with these outcomes in either group.

5.2 BNP in patients requiring mechanical support after cardiac surgery

Chikovani and colleagues studied the potential utility of BNP levels in the assessment of native myocardial performance in ten neonates and infants being supported with

extracorporeal life support (ECLS) after cardiac surgery(Chikovani et al. 2007). In particular, alterations in BNP during weaning trials off of ECLS were determined and compared to other biochemical markers, including lactate and the $AVDO_2$.This study did not find associations between long-term outcome and alterations in lactate and the $AVDO_2$ during trials off ECLS. However, an increase in BNP during the final trial off ECLS had a sensitivity of 80% and a specificity of 100% for predicting the need for an unplanned operation or death within 3 months. A notable finding of this study was that BNP levels decreased during trials off of ECLS support (which were accomplished through the use of a bridge placed in the ECLS circuit, allowing mechanical support to be diverted away from the patient before the ECLS cannulae were removed) in patients who were successfully separated from ECLS after a trial. Since trials off ECLS were associated with increased cardiac filling (increased central venous pressures) in all patients, this study suggests that BNP levels may be regulated by additional mechanisms (other than just myocyte stretch). Furthermore, during trials off of ECLS, inotropic support, lactate levels and the $AVDO_2$ increased in all patients (both those who successfully separated from ECLS and those who did not), suggesting that BNP levels may capture myocardial performance in a unique manner.

In a similar earlier study, Huang and colleagues studied fifteen pediatric patients requiring ECLS for cardiogenic shock(Huang et al. 2006). Eleven of the fifteen patients developed shock after cardiac surgery. These investigators did not find an association between BNP levels during the course of ECLS and survival after ECLS. However, they did find that BNP levels on the first and fourth day following separation from ECLS were significantly higher in nonsurvivors than survivors(Huang et al. 2006).

5.3 Long-term outcomes

Koch and colleagues measured BNP levels in 130 children and adolescents (mean age of 16.1 years) with a history of surgically repaired tetralogy of Fallot, at a mean time of 13±6.5 years after repair. They also performed exercise testing and echocardiograms. BNP levels were increased above normal gender and age specific values in 60% of the patients, but were less than 200 pg/ml in all patients(Koch et al. 2010). BNP levels were higher in patients awaiting pulmonary valve replacement, and in those in NYHA class II compared to class I. Furthermore, BNP levels correlated with right ventricular dilatation and the severity of tricuspid and pulmonary valve regurgitation, and were inversely correlated with exercise time. In addition, BNP levels increased over time in patients awaiting pulmonary valve replacement and decreased after surgery. The authors suggested that BNP levels might aid in the long-term management of these patients, particularly in the timing of pulmonary valve replacement.

Pietrzak and Werner conducted a similar study, in which they measured NT-proBNP levels in 20 adolescents (10 to 17 years of age) during a follow-up period of 7 to 16 years after repair of tetralogy of Fallot(Pietrzak and Werner 2009). They found that NT-proBNP levels were higher in those patients than in age matched healthy controls. NT-proBNP levels were higher in patients who had undergone repair with a transannular patch compared to those who underwent repair without a transannular patch. Furthermore, NT-proBNP levels were increased in patients with: QRS prolongation during exercise testing, severe pulmonary regurgitation, and severe triscuspid regurgitation. Likewise, Dodge-Khatami and colleagues measured plasma NT-proBNP levels and obtained cardiac magnetic resonance imaging in

23 patients with repaired tetralogy of Fallot, severe pulmonary insufficiency, and increased right ventricular end-diastolic volume that were undergoing pulmonary valve replacement(Dodge-Khatami et al. 2006). Log-NT-proBNP levels were inversely correlated with right ventricular ejection fraction before and 6 months after surgery. NT-proBNP levels, right ventricular end-diastolic volume, and pulmonary insufficiency all decreased by 6 months after surgery.

These three studies differed from a study by Apitz and colleagues. These investigators measured BNP levels and recorded pressure-volume loops using conductance catheters in 16 adolescents (median age of 14.2 years) with a known history of right ventricular dilation (NYHA class I, and Ross class 0) secondary to pulmonary regurgitation after repair of tetralogy of Fallot(Apitz et al. 2009). Latent right ventricular dysfunction was defined as impaired contractility (calculated by the slope of the end-systolic pressure-volume relation) in response to a dobutamine infusion. Latent right ventricular dysfunction was identified in 5 patients, but no clear relationship with BNP levels could be observed. The difference between this study and those of Koch, Pietrzak, and Dodge-Khatami may relate to the severity of disease, suggesting that BNP may not be useful in detecting subclinical deterioration in this patient population.

In a small pilot study, Paul and colleagues measured BNP levels before and after surgical repair of ventricular septal defects in 14 patients who were less than 2 years of age(Paul et al. 2009). Mean BNP levels decreased by 94 pg/ml after repair. Longitudinal analysis found that there was a weak inverse correlation between the postoperative change in BNP and postoperative weight gain (weight z-score change per month).

Recently, Atz and colleagues described their findings in a study of 510 children (6-18 years of age), who were enrolled in the Pediatric Heart Network Fontan cross-sectional study(Atz et al. 2011). The patients had all undergone 3rd stage palliation of single ventricle cardiac defects with a Fontan procedure (median time from Fontan of 8.2 years). The distribution of BNP levels in these patients were highly skewed, but were generally within the normal range (median 13 pg/ml). However, logBNP levels were independently associated with a history of pre-Fontan systolic dysfunction, and post-Fontan complications, including thrombosis. LogBNP levels were higher in patients with atrial-to-pulmonary connections compared to extracardiac conduits. Furthermore, increased logBNP levels were associated with a lower level of physical functioning, chronotropic index during exercise, diastolic dysfunction, and greater ventricular mass measured by cardiac magnetic resonance imaging.

In a similar study, Koch and colleagues measured plasma BNP levels in 67 patients after a modified Fontan procedure(Koch et al. 2008). Although there was a wide range, BNP levels were normal in 81% of the patients, with a median value of 13 pg/ml. Levels were not different between patients with right or left ventricular morphology. BNP levels were higher in patients in NYHA class II compared to those in class I, and were positively correlated with the severity of AV valve regurgitation. Likewise, Man and colleagues measured plasma BNP levels and assessed ventricular function (by tissue Doppler assessments, acoustic quantification, and myocardial performance index) in 35 asymptomatic patients who had previously undergone a Fontan procedure(Man and Cheung 2007). Comparisons were made to 34 healthy controls. Although BNP levels were low in the Fontan group (median 21 pg/ml), they were higher than the control group. Moreover, BNP levels were inversely correlated with ventricular function, particularly diastolic function.

6. Conclusion

The essential relationship between BNP production by the cardiac ventricle and increased myocyte stretch is the foundation for the potential use of BNP as a biomarker in any condition in which abnormal ventricular loading conditions are primarily involved in the pathophysiology. To date, plasma BNP determinations have not attained the same clinical prominence in pediatric patients as in adults. The growing utilization of BNP determinations in the care of adult patients likely stems from the ability to make clinical decisions, indeed to titrate therapy, in response to BNP levels(Troughton et al. 2000). Thus, a widespread use of BNP in pediatric patients is restrained by the scarcity of data that supports BNP guided therapies. It is likely that this discrepancy between the adult and pediatric experience relates, in part, to the number of investigations. However, compared to adult CHF, pediatric cardiac diseases resulting in ventricular dysfunction and CHF are far more heterogeneous. In fact, coronary artery disease is the leading cause of CHF in adults, whereas pediatric CHF may result from a wide spectrum of congenital cardiac defects and various cardiomyopathies. Moreover, clinically relevant cutoff values for plasma BNP levels within these various disease processes are not well established or are completely unknown. Nonetheless, the ability to readily quantify plasma BNP levels is attractive as few markers are so directly related to the pathobiology of the cardiac ventricle. This is particularly true in the management of critically ill pediatric patients, where we often employ surrogate markers of disease severity, such as serum lactate levels, that reflect global processes as opposed to organ specific functioning.

Based on the studies outlined above, it is clear that BNP determinations can offer valuable clinical information to aid in the management of neonates, infants, and children undergoing surgical repair of cardiac defects. It is also clear, however, that the information is unlikely to come from single cut-off values that can be generalized across populations. Rather, a clinical utility for BNP determinations will likely come from an advanced understanding of expected perioperative patterns of change in BNP levels – patterns that will differ between age groups and specific cardiac defects. Furthermore, future studies must begin to evaluate the utility of guiding therapy in response to plasma BNP values. Fortunately, the ease of measuring BNP levels should facilitate these studies. For now the available data demonstrate that BNP has emerged as a novel biomarker with great potential.

7. References

Apitz, C., L. Sieverding, H. Latus, A. Uebing, S. Schoof, and M. Hofbeck. 2009. "Right ventricular dysfunction and B-type natriuretic peptide in asymptomatic patients after repair for tetralogy of Fallot." *Pediatric cardiology* no. 30 (7):898-904. doi: 10.1007/s00246-009-9453-y.

Ationu, A., and N. D. Carter. 1993. "Brain and atrial natriuretic peptide plasma concentrations in normal healthy children." *Br J Biomed Sci* no. 50 (2):92-5.

Ationu, A., D. R. Singer, A. Smith, M. Elliott, M. Burch, and N. D. Carter. 1993. "Studies of cardiopulmonary bypass in children: implications for the regulation of brain natriuretic peptide." *Cardiovasc Res* no. 27 (8):1538-41.

Atz, A. M., V. Zak, R. E. Breitbart, S. D. Colan, S. K. Pasquali, D. T. Hsu, M. Lu, L. Mahony, S. M. Paridon, M. D. Puchalski, T. Geva, and B. W. McCrindle. 2011. "Factors

Associated with Serum Brain Natriuretic Peptide Levels after the Fontan Procedure." *Congenital heart disease*. doi: 10.1111/j.1747-0803.2011.00496.x.

Berry, J. G., B. Askovich, R. E. Shaddy, J. A. Hawkins, and C. G. Cowley. 2007. "Prognostic Value of B-Type Natriuretic Peptide in Surgical Palliation of Children with Single-Ventricle Congenital Heart Disease." *Pediatr Cardiol*.

Cannesson, M., C. Bionda, B. Gostoli, O. Raisky, S. di Filippo, D. Bompard, C. Vedrinne, R. Rousson, J. Ninet, J. Neidecker, and J. J. Lehot. 2007. "Time course and prognostic value of plasma B-type natriuretic peptide concentration in neonates undergoing the arterial switch operation." *Anesth Analg* no. 104 (5):1059-65, tables of contents.

Cantinotti, M., S. Storti, A. Ripoli, L. Zyw, M. Crocetti, N. Assanta, B. Murzi, and A. Clerico. 2010. "Diagnostic accuracy of B-type natriuretic hormone for congenital heart disease in the first month of life." *Clinical chemistry and laboratory medicine : CCLM / FESCC* no. 48 (9):1333-8. doi: 10.1515/CCLM.2010.251.

Chikovani, O., J. Hsu, R. Keller, TR. Karl, A. Azakie, I. Adatia, P. Oishi, and JR. Fineman. 2007. "B-type natriuretic peptide levels predict outcomes for children on extracorporeal life support after cardiac surgery." *J Thorac Cardiovasc Surg*:In Press.

Choi, B. M., K. H. Lee, B. L. Eun, K. H. Yoo, Y. S. Hong, C. S. Son, and J. W. Lee. 2005. "Utility of rapid B-type natriuretic peptide assay for diagnosis of symptomatic patent ductus arteriosus in preterm infants." *Pediatrics* no. 115 (3):e255-61.

Costello, J. M., C. L. Backer, P. A. Checchia, C. Mavroudis, R. G. Seipelt, and D. M. Goodman. 2004. "Alterations in the natriuretic hormone system related to cardiopulmonary bypass in infants with congestive heart failure." *Pediatr Cardiol* no. 25 (4):347-53.

Costello, J. M., D. M. Goodman, and T. P. Green. 2006. "A review of the natriuretic hormone system's diagnostic and therapeutic potential in critically ill children." *Pediatr Crit Care Med* no. 7 (4):308-18.

da Graca, R. L., D. C. Hassinger, P. A. Flynn, C. P. Sison, M. Nesin, and P. A. Auld. 2006. "Longitudinal changes of brain-type natriuretic peptide in preterm neonates." *Pediatrics* no. 117 (6):2183-9.

Das, B. B. 2010. "Plasma B-type natriuretic peptides in children with cardiovascular diseases." *Pediatric cardiology* no. 31 (8):1135-45. doi: 10.1007/s00246-010-9758-x.

de Bold, A. J., H. B. Borenstein, A. T. Veress, and H. Sonnenberg. 1981. "A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats." *Life Sci* no. 28 (1):89-94.

Dodge-Khatami, A., E. V. Buchel, W. Knirsch, A. Kadner, V. Rousson, H. H. Dave, U. Bauersfeld, and R. Pretre. 2006. "Brain natriuretic peptide and magnetic resonance imaging in tetralogy with right ventricular dilatation." *The Annals of thoracic surgery* no. 82 (3):983-8. doi: 10.1016/j.athoracsur.2006.03.038.

Fellahi, J. L., G. Daccache, D. Rubes, M. Massetti, J. L. Gerard, and J. L. Hanouz. 2011. "Does preoperative B-type natriuretic peptide better predict adverse outcome and prolonged length of stay than the standard European System for Cardiac Operative Risk Evaluation after cardiac surgery?" *Journal of cardiothoracic and vascular anesthesia* no. 25 (2):256-62. doi: 10.1053/j.jvca.2010.05.009.

Flynn, P. A., R. L. da Graca, P. A. Auld, M. Nesin, and C. S. Kleinman. 2005. "The use of a bedside assay for plasma B-type natriuretic peptide as a biomarker in the management of patent ductus arteriosus in premature neonates." *J Pediatr* no. 147 (1):38-42.

Gessler, P., W. Knirsch, B. Schmitt, V. Rousson, and A. von Eckardstein. 2006. "Prognostic value of plasma N-terminal pro-brain natriuretic peptide in children with congenital heart defects and open-heart surgery." *J Pediatr* no. 148 (3):372-6.

Hama, N., H. Itoh, G. Shirakami, O. Nakagawa, S. Suga, Y. Ogawa, I. Masuda, K. Nakanishi, T. Yoshimasa, Y. Hashimoto, and et al. 1995. "Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction." *Circulation* no. 92 (6):1558-64.

Holmgren, D., A. Westerlind, H. Berggren, P. A. Lundberg, and H. Wahlander. 2008. "Increased natriuretic peptide type B level after the second palliative step in children with univentricular hearts with right ventricular morphology but not left ventricular morphology." *Pediatric cardiology* no. 29 (4):786-92. doi: 10.1007/s00246-008-9201-8.

Holmstrom, H., and T. Omland. 2002. "Natriuretic peptides as markers of patent ductus arteriosus in preterm infants." *Clin Sci (Lond)* no. 103 (1):79-80.

Hsu, J. H., P. E. Oishi, R. L. Keller, O. Chikovani, T. R. Karl, A. Azakie, I. Adatia, and J. R. Fineman. 2008. "Perioperative B-type natriuretic peptide levels predict outcome after bidirectional cavopulmonary anastomosis and total cavopulmonary connection." *J Thorac Cardiovasc Surg* no. 135 (4):746-53.

Hsu, J., R. Keller, O. Chikovani, H. Cheng, SA. Hollander, TR. Karl, A. Azakie, I. Adatia, P. Oishi, and JR. Fineman. 2007. "B-type natriuretic peptide levels predict outcome after neonatal cardiac surgery." *J Thorac Cardiovasc Surg*:In Press.

Huang, S. C., E. T. Wu, W. J. Ko, L. P. Lai, J. Hsu, C. I. Chang, I. S. Chiu, S. S. Wang, M. H. Wu, F. Y. Lin, and Y. S. Chen. 2006. "Clinical implication of blood levels of B-type natriuretic peptide in pediatric patients on mechanical circulatory support." *Ann Thorac Surg* no. 81 (6):2267-72.

Inuzuka, R., S. Tatebe, S. Wakiguchi, H. Nakajima, H. Ohtsu, K. Dimopoulos, and H. Aotsuka. 2011. "B-type natriuretic peptide at the early stage of univentricular circulation reflects inadequate adaptation to volume overload." *International journal of cardiology*. doi: 10.1016/j.ijcard.2011.02.023.

Knirsch, W., E. Hausermann, M. Fasnacht, M. Hersberger, P. Gessler, and U. Bauersfeld. 2011. "Plasma B-type natriuretic peptide levels in children with heart disease." *Acta paediatrica*. doi: 10.1111/j.1651-2227.2011.02258.x.

Koch, A., T. Kitzsteiner, S. Zink, R. Cesnjevar, and H. Singer. 2006. "Impact of cardiac surgery on plasma levels of B-type natriuretic peptide in children with congenital heart disease." *Int J Cardiol*.

Koch, A. M., M. Rauh, S. Zink, and H. Singer. 2006. "Decreasing ratio of plasma N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide according to age." *Acta Paediatr* no. 95 (7):805-9.

Koch, A. M., S. Zink, M. Glockler, T. Seeliger, and S. Dittrich. 2010. "Plasma levels of B-type natriuretic peptide in patients with tetralogy of Fallot after surgical repair." *International journal of cardiology* no. 143 (2):130-4. doi: 10.1016/j.ijcard.2009.01.062.

Koch, A. M., S. Zink, and H. Singer. 2008. "B-type natriuretic peptide in patients with systemic right ventricle." *Cardiology* no. 110 (1):1-7. doi: 10.1159/000109399.

Koch, A. M., S. Zink, H. Singer, and S. Dittrich. 2008. "B-type natriuretic peptide levels in patients with functionally univentricular hearts after total cavopulmonary connection." *European journal of heart failure* no. 10 (1):60-2. doi: 10.1016/j.ejheart.2007.11.001.

Koch, A., and H. Singer. 2003. "Normal values of B type natriuretic peptide in infants, children, and adolescents." *Heart* no. 89 (8):875-8.

Koch, A., S. Zink, and H. Singer. 2006. "B-type natriuretic peptide in paediatric patients with congenital heart disease." *Eur Heart J* no. 27 (7):861-6.

Kunii, Y., M. Kamada, S. Ohtsuki, T. Araki, K. Kataoka, M. Kageyama, N. Nakagawa, and Y. Seino. 2003. "Plasma brain natriuretic peptide and the evaluation of volume overload in infants and children with congenital heart disease." *Acta Med Okayama* no. 57 (4):191-7.

Law, Y. M., A. W. Hoyer, M. D. Reller, and M. Silberbach. 2009. "Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular disease in children: the Better Not Pout Children! Study." *Journal of the American College of Cardiology* no. 54 (15):1467-75. doi: 10.1016/j.jacc.2009.06.020.

Levin, E. R., D. G. Gardner, and W. K. Samson. 1998. "Natriuretic peptides." *N Engl J Med* no. 339 (5):321-8.

Mainwaring, R. D., C. Parise, S. B. Wright, A. L. Juris, R. A. Achtel, and H. Fallah. 2007. "Brain natriuretic peptide levels before and after ventricular septal defect repair." *The Annals of thoracic surgery* no. 84 (6):2066-9. doi: 10.1016/j.athoracsur.2007.07.021.

Maisel, A. S., P. Krishnaswamy, R. M. Nowak, J. McCord, J. E. Hollander, P. Duc, T. Omland, A. B. Storrow, W. T. Abraham, A. H. Wu, P. Clopton, P. G. Steg, A. Westheim, C. W. Knudsen, A. Perez, R. Kazanegra, H. C. Herrmann, and P. A. McCullough. 2002. "Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure." *N Engl J Med* no. 347 (3):161-7.

Man, B. L., and Y. F. Cheung. 2007. "Plasma brain natriuretic peptide and systemic ventricular function in asymptomatic patients late after the Fontan procedure." *Heart and vessels* no. 22 (6):398-403. doi: 10.1007/s00380-007-0993-x.

McGrath, M. F., M. L. de Bold, and A. J. de Bold. 2005. "The endocrine function of the heart." *Trends Endocrinol Metab* no. 16 (10):469-77.

Mitchell, J., and S. T. Webb. 2011. "Is brain natriuretic peptide a marker for adverse postoperative outcomes in patients undergoing cardiac surgery?" *Interactive cardiovascular and thoracic surgery* no. 12 (3):467-72. doi: 10.1510/icvts.2010.252601.

Niedner, M. F., J. L. Foley, R. H. Riffenburgh, D. P. Bichell, B. M. Peterson, and A. Rodarte. 2010. "B-type natriuretic peptide: perioperative patterns in congenital heart disease." *Congenital heart disease* no. 5 (3):243-55. doi: 10.1111/j.1747-0803.2010.00396.x.

Ozhan, H., S. Albayrak, H. Uzun, S. Ordu, A. Kaya, and M. Yazici. 2007. "Correlation of plasma B-type natriuretic peptide with shunt severity in patients with atrial or ventricular septal defect." *Pediatric cardiology* no. 28 (4):272-5. doi: 10.1007/s00246-006-0014-3.

Paul, M. A., C. L. Backer, H. J. Binns, C. Mavroudis, C. L. Webb, R. Yogev, and W. H. Franklin. 2009. "B-type natriuretic peptide and heart failure in patients with ventricular septal defect: a pilot study." *Pediatric cardiology* no. 30 (8):1094-7. doi: 10.1007/s00246-009-9503-5.

Perez-Piaya, M., E. Abarca, V. Soler, A. Coca, M. Cruz, F. Villagra, S. Giannivelli, and A. Asensio. 2011. "Levels of N-terminal-pro-brain natriuretic peptide in congenital heart disease surgery and its value as a predictive biomarker." *Interactive cardiovascular and thoracic surgery* no. 12 (3):461-6. doi: 10.1510/icvts.2010.245803.

Pietrzak, R., and B. Werner. 2009. "Usefulness of NT-proBNP in assessment of right ventricular function in children after tetralogy of Fallot correction - a preliminary study." *Kardiologia polska* no. 67 (4):378-83.

Price, J. F., A. K. Thomas, M. Grenier, B. W. Eidem, E. O'Brian Smith, S. W. Denfield, J. A. Towbin, and W. J. Dreyer. 2006. "B-type natriuretic peptide predicts adverse

cardiovascular events in pediatric outpatients with chronic left ventricular systolic dysfunction." *Circulation* no. 114 (10):1063-9.

Puddy, V. F., C. Amirmansour, A. F. Williams, and D. R. Singer. 2002. "Plasma brain natriuretic peptide as a predictor of haemodynamically significant patent ductus arteriosus in preterm infants." *Clin Sci (Lond)* no. 103 (1):75-7.

Rodseth, R. N., L. Padayachee, and B. M. Biccard. 2008. "A meta-analysis of the utility of pre-operative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients." *Anaesthesia* no. 63 (11):1226-33. doi: 10.1111/j.1365-2044.2008.05574.x.

Sanjeev, S., M. Pettersen, J. Lua, R. Thomas, S. Shankaran, and T. L'Ecuyer. 2005. "Role of plasma B-type natriuretic peptide in screening for hemodynamically significant patent ductus arteriosus in preterm neonates." *J Perinatol* no. 25 (11):709-13.

Shah, A., A. M. Feraco, C. Harmon, T. Tacy, J. R. Fineman, and H. S. Bernstein. 2009. "Usefulness of various plasma biomarkers for diagnosis of heart failure in children with single ventricle physiology." *The American journal of cardiology* no. 104 (9):1280-4. doi: 10.1016/j.amjcard.2009.06.046.

Shih, C. Y., A. Sapru, P. Oishi, A. Azakie, T. R. Karl, C. Harmon, R. Asija, I. Adatia, and J. R. Fineman. 2006. "Alterations in plasma B-type natriuretic peptide levels after repair of congenital heart defects: a potential perioperative marker." *J Thorac Cardiovasc Surg* no. 131 (3):632-8.

Silver, M. A., A. Maisel, C. W. Yancy, P. A. McCullough, J. C. Burnett, Jr., G. S. Francis, M. R. Mehra, W. F. th Peacock, G. Fonarow, W. B. Gibler, D. A. Morrow, and J. Hollander. 2004. "BNP Consensus Panel 2004: A clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases." *Congest Heart Fail* no. 10 (5 Suppl 3):1-30.

Suda, K., M. Matsumura, and M. Matsumoto. 2003. "Clinical implication of plasma natriuretic peptides in children with ventricular septal defect." *Pediatr Int* no. 45 (3):249-54.

Sudoh, T., K. Kangawa, N. Minamino, and H. Matsuo. 1988. "A new natriuretic peptide in porcine brain." *Nature* no. 332 (6159):78-81.

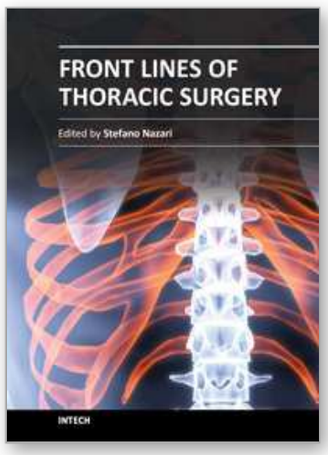
Sun, L. S., C. Dominguez, N. A. Mallavaram, and J. M. Quaegebeur. 2005. "Dysfunction of atrial and B-type natriuretic peptides in congenital univentricular defects." *J Thorac Cardiovasc Surg* no. 129 (5):1104-10.

Troughton, R. W., C. M. Frampton, T. G. Yandle, E. A. Espiner, M. G. Nicholls, and A. M. Richards. 2000. "Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations." *Lancet* no. 355 (9210):1126-30.

Yandle, T. G. 1994. "Biochemistry of natriuretic peptides." *J Intern Med* no. 235 (6):561-76.

Yoshibayashi, M., T. Kamiya, Y. Saito, K. Nakao, K. Nishioka, S. Temma, H. Itoh, G. Shirakami, and H. Matsuo. 1995. "Plasma brain natriuretic peptide concentrations in healthy children from birth to adolescence: marked and rapid increase after birth." *Eur J Endocrinol* no. 133 (2):207-9.

Zhang, Y., D. Carreras, and A. J. de Bold. 2003. "Discoordinate re-expression of cardiac fetal genes in N(omega)-nitro-L-arginine methyl ester (L-NAME) hypertension." *Cardiovasc Res* no. 57 (1):158-67.



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Front Lines of Thoracic Surgery collects up-to-date contributions on some of the most debated topics in today's clinical practice of cardiac, aortic, and general thoracic surgery,and anesthesia as viewed by authors personally involved in their evolution. The strong and genuine enthusiasm of the authors was clearly perceptible in all their contributions and I'm sure that will further stimulate the reader to understand their messages. Moreover, the strict adhesion of the authors' original observations and findings to the evidence base proves that facts are the best guarantee of scientific value. This is not a standard textbook where the whole discipline is organically presented, but authors' contributions are simply listed in their pertaining subclasses of Thoracic Surgery. I'm sure that this original and very promising editorial format which has and free availability at its core further increases this book's value and it will be of interest to healthcare professionals and scientists dedicated to this field.

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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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