REVIEW

Are B-type natriuretic peptide (BNP) and N-terminal-pro-BNP useful in neonates?

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B-type natriuretic peptide (BNP) and N-terminal-pro-BNP (NTpBNP) have a major role in screening and diagnosis of cardiac disease and monitoring of the treatment response in children and adults. This review discusses the evidence underpinning the potential benefits of these natriuretic peptides in neonatology. They may serve as a useful adjunct to echocardiography in the diagnosis of patent ductus arteriosus and its response to treatment and the diagnosis of persistent pulmonary hypertension of the newborn. However, more work is needed to explore the possible roles of BNP/NTpBNP in the management of sepsis and monitoring of cardiac performance in neonates.

Natriuretic peptides are ring-shaped amino acid sequences with various actions. Four natriuretic peptides have been described to date, namely A, B, C and D.[1] Atrial natriuretic peptide (ANP) is synthesised by and released from atrial myocytes. It lowers the blood pressure and has diuretic, natriuretic and kaliuretic properties. Brain natriuretic peptide was named as such following its discovery in porcine brains.[2] However, there is a much higher concentration in the ventricles of the heart, hence the current name B-type natriuretic peptide (BNP).[3] C-type natriuretic peptide is found in the brain and coronary vessels. It regulates vascular tone and lacks natriuretic properties.[4] Dendroaspis natriuretic peptide (DNP) is found in snake venom and there is high affinity between DNP and natriuretic peptide receptor A. It has no known function in humans.[5]

PHYSIOLOGY OF BNP AND NTpBNP

BNP has a 32 amino acid ring structure, and the sequence is present on chromosome 1. It acts on a cyclic guanosine monophosphate (cGMP)-coupled receptor via a transmembrane domain.[6] The ring structure must remain intact to ensure receptor binding to natriuretic peptide receptors A and B (NPR-A/B). The ventricles of the heart are the main site of BNP synthesis and release in response to volume and pressure loading, and ventricular stress. Pro-BNP, the inactive precursor, is cleaved into BNP, the active component, and N-terminal-pro-BNP (NTpBNP), an inactive byproduct. The half-life of BNP is 20 min and of NTpBNP is 60 min.[7] The instability of BNP messenger-RNA renders storage difficult and acts as regulator of serum BNP levels.

BNP causes diuresis, natriuresis, arterial and venous vasodilatation, and it antagonises the renin–angiotensin system. The net effect is a reduction of intravascular volume, and ventricular preload and afterload. Recently, it has been associated with the regulation of pulmonary vasculature, possibly including the ductus arteriosus.[8 9] BNP is excreted after cleavage by membrane-bound neutral peptidase, which is found in the kidneys and vascular tree. It is also cleared from the blood by direct binding to the natriuretic peptide receptor C, endocytosis and lysosomal degradation.[10]

CLINICAL ROLE OF BNP

BNP and NTpBNP are easily measured with commercially available kits including bedside tests. Clinical studies have shown excellent correlation between BNP and NTpBNP levels in both adult and cord blood.[11–13] In adults, BNP is associated with poor ventricular function. Furthermore, the possible link between natriuretic peptides and sepsis may lead to better understanding of the mechanisms involved in cardiogenic shock.[14] Recent research has concentrated on the potential use of these markers in paediatric and neonatal medicine.

Conventional methods of clinical and radiological assessment have poor diagnostic sensitivity to differentiate between cardiac and non-cardiac causes of dyspnoea. Moreover, echocardiography may not be readily available in some institutions. BNP and NTpBNP are good screening tools that detect chronic ventricular dysfunction, with sensitivities and specificities surpassing those of clinical and radiological methods.[15] They are useful in the diagnosis of congestive heart failure in dyspnoeic patients presenting to the emergency department.[11] In addition, these markers facilitate screening, treatment response and prognosis in asymptomatic patients with subclinical left ventricular dysfunction.[16–18]

Although not as common as in adults, heart disease is a significant cause of morbidity and mortality in infants and children. BNP and NTpBNP levels are raised in children with heart disease, leading to increased ventricular pressure and volume loading.[19 20] The NTpBNP/BNP ratio decreases with increasing age, reflecting age-dependent differences in metabolic clearance of both peptides—an important consideration for

Abbreviations: BNP, B-type natriuretic peptide; NTpBNP, N-terminal-pro-BNP; PPHN, persistent pulmonary hypertension of the newborn

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comparison studies.[21] In addition, plasma BNP correlates closely with shunt volume in left-to-right cardiac lesions, increases with decreasing left ventricular ejection fraction and correlates positively with increasing right ventricular systolic pressures.[22] NTpBNP levels are useful for distinguishing between acute and chronic left ventricular dysfunction (mean levels 65 600 pg/ml and 1125 pg/ml, respectively).[23] The levels can also reflect functional capacity in children with congestive heart failure.[19] In children with dilated cardiomyopathy NTpBNP is a good marker for persistent left ventricular dysfunction with levels normalising in children whose ventricular function shows improvement on echocardiography.[24] In infants with respiratory distress, measurement of plasma NTpBNP can differentiate between acute heart failure and lung disease, and it can be used to monitor response to treatment.[25]

Raised level of NTpBNP preoperatively in children undergoing open heart surgery are linked with complicated postoperative outcomes.[26] A cytoprotective role has been suggested for BNP based on the observation of persistently high levels after cardiac surgery.[27] BNP levels tend to be higher in children receiving long-term immunosuppressive treatment following liver transplantation than in healthy controls, despite the lack of echocardiographic evidence of cardiac compromise. This suggests that BNP levels help to identify patients with early cardiac damage.[28]

Limited data have demonstrated the potential benefit of these peptides as markers of cyanotic and obstructive lesions. Cowley *et al* found a significant correlation between left ventricle to aorta gradient and BNP levels.[29] In patients with aortic stenosis, NTpBNP has been used to monitor response to valve replacement.[30] In a recent study, Hopkins *et al* found higher levels of NTpBNP in 10 adult patients with cyanotic heart disease (including Eisenmenger's syndrome) despite lack of ventricular pressure loading.[31]

APPLICATION OF BNP AND NTpBNP IN NEONATES

Levels of BNP and NTpBNP surge at birth, plateauing on days 3–4. This is followed by a steady fall to reach a constant level in infancy.[32] The surge is probably multifactorial including the loss of the placental low pressure system. Exposure to the initially supra-systemic pulmonary pressures subjects the ventricle to greater volume and pressure loading. Furthermore, the placenta has a role in clearance of natriuretic peptides and loss of this clearance system contributes to the high levels.[33] Therefore high levels of BNP at birth have a crucial regulatory role in the haemodynamic changes associated with transition to extrauterine life. Kidney maturation, a rise in systemic vascular resistance and a fall in pulmonary pressures explain the subsequent fall in the peptide levels.

Several characteristics distinguish the premature neonatal heart from that of older infants. The neonatal myocardium has a higher water concentration and a greater proportion of ''stiff'' collagen resulting in a non-compliant ventricle and diastolic dysfunction with relatively poor ventricular filling.[34] The relatively higher heart rate in neonates can compound this problem. Therefore adequate left ventricular function in neonates may be essential to maintain adequate systemic perfusion. However conventional bedside measurements of cardiac function, such as blood pressure monitoring may not accurately reflect systemic perfusion.[35] BNP may indicate the degree of ventricular function and reduce the reliance on echocardiography.

NORMAL VALUES OF BNP AND NTpBNP IN NEONATES

There is a paucity of normative values of BNP and NTpBNP in neonates (tables 1 and 2). Reference ranges quoted in the literature vary depending on timing of the test, the kits used and the population investigated. Natriuretic peptides are thought not to cross the placenta and therefore any variation in neonates must be explained intrinsically.[38]

ROLE BNP AND NTpBNP IN THE MANAGEMENT OF PATENT DUCTUS ARTERIOSUS

Recent animal studies have examined a possible pathophysiological association between BNP and postnatal ductal patency. Ductal tissue from fetal and newborn mice shows a changing pattern of expression of natriuretic peptide receptors. Fetal ductal tissue has a higher ratio of NPR-A/B (maintains ductal patency) to NPR-C (responsible for degradation). This ratio reverses in the ductal tissue of the newborn mouse suggesting that vasodilatory effects in the fetus are reduced after birth by ligand internalisation.[8] These findings provide the first evidence for the possible pathological role of BNP in maintaining ductal patency after birth. They suggest that elevated levels of natriuretic peptide due to patent ductus arteriosus (PDA) or other factors act in a harmful feed-forward mechanism inhibiting ductal closure after birth. Identification of other factors which contribute to BNP production may aid in better, more physiological management of a PDA.

BNP may be a useful screening tool for the presence of a PDA in premature neonates as levels of BNP are high in the presence of a significantly patent duct. Flynn *et al* showed that BNP correlated well with ductal size ($r = 0.62$), increased pulmonary flow ($r = 0.63$) and increased steal (retrograde diastolic flow) in the descending aorta and the superior mesenteric artery ($r = 0.54$ and 0.41, respectively). However, they found a poor correlation between left atrial to aortic ratio (LA:Ao ratio) and BNP levels ($r = 0.33$).[43] Choi *et al* found a stronger correlation

Table 1 Reference ranges for B-type natriuretic peptide (BNP) in neonates

Study	Number of subjects	Age range Source	Kit	BNP levels
Koch and Singer[36]	12	Day 0 to day 1 Plasma	Biosite*	Mean: 231.6 pg/ml SD: 197.5
Koch and Singer[36]	14	Day 4 to day 6 Plasma	Biosite	Mean: 48.4 pg/ml SD: 49.1
Kunii *et al*[37]	11	Day 0 Cord blood	Shiono RIA BNP†	Mean: 10.4 pg/ml SD: 11.9
Kunii *et al*[37]	11	Day 1 Plasma	Shiono RIA BNP	Mean: 118.8 pg/ml SD: 83.2
Kunii *et al*[37]	11	Day 7 Plasma	Shiono RIA BNP	Mean: 15.3 pg/ml SD: 7.8
Soldin *et al*[12]	50	<31 days Plasma	Biosite	97.5th percentile: 1585 pg/ml

*Biosite, San Diego, USA; †Shiono RIA BNP, Shionogi, Osaka, Japan.

Table 2 Reference ranges for N-terminal-pro-B-type natriuretic peptide (NTpBNP) in neonates

Study	Number of subjects	Age range Source	Kit	NTpBNP levels
Mir *et al*[32]	153	Day 1 Venous/cord	Biomedica*	Mean:641 fmol/mL Range: 254–1272
Mir *et al*[39]	153	Day 3 Venous/cord	Biomedica	Mean: 246 fmol/ml Range: 110–430
Schwachtgen *et al*[39]	62	Day 1 Cord blood	ECLIA† Roche‡	Mean: 818 pg/ml Range: 281–2595
Bar-Oz *et al*[38]	122	Day 1 Cord blood	Elecsys¶ 1010/2010¶	Mean: 578.8 ng/l SD: 351.3
Bar Oz *et al*[38]	33	Day 1 Plasma	Elecsys 1010/2010	Mean: 3042.4 ng/l SD: 1783.2
Hammerer-Lercher *et al*[40]	42	Day 1 Cord blood	Elecsys 1010	Mean: 553.4 ng/l 25th–75th: 413.5–832.9 ng/l
Bakker *et al*[41]	67	32–42 wk Cord blood	Elecsys 2010	Mean: 79.5 pmol/l SD: 42.9
Rauh *et al*[42]	13	<1 month Plasma	Elecsys	Range: 1121–7740 ng/l
Soldin *et al*[12]	40 boys	<31 days Plasma	Dade RxL Dimension§	97.5th percentile: 28 184 pg/ml
Soldin *et al*[12]	53 girls	<31 days Plasma	Dade RxL Dimension	97.5th percentile: 35 481 pg/ml

*Biomedica, Oxford, UK; †ECLIA, Roche Diagnostics, Basel, Switzerland; ‡Roche, Basel, Switzerland; ¶Elecsys 1010/2010, Kansas, USA; §Dade RxL Dimension, Massachusetts, USA.

($r = 0.73$).[44] The difference might be due to the degree of hydration of the infants. Dehydrated or fluid-restricted neonates may have a smaller left atrium, and thus a reduced LA:Ao ratio and altered relationship with BNP. There is a wide variation in the levels of BNP associated with a significant PDA (range 70–1110 pg/ml).[44–47] This raises the possibility of further unidentified factors influencing BNP levels.

BNP has also been shown to be useful in monitoring treatment response to medical PDA ligation, with falling levels comparable with those in preterm neonates without a PDA.[44] Ductal closure cannot alone be responsible for the fall in BNP levels, and some neonates have low BNP levels despite a large haemodynamically significant duct.[45 46] The exact mechanisms of these neonatal phenomena are still unclear.

Although BNP may not replace echo in the diagnosis of PDA, it may obviate the need for repeated echocardiography to confirm ductal closure following treatment. The use of NTpBNP to detect PDA and monitor treatment is yet to be explored. NTpBNP may serve as a better marker than BNP because of its better stability and longer half-life. There are no bedside assays available for NTpBNP, although BNP can be measured using a bedside device.

BNP AND MANAGEMENT OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Pulmonary vascular resistance may remain elevated during the neonatal period leading to difficulties in oxygenation and persistent pulmonary hypertension of the newborn (PPHN). Echocardiography helps distinguish PPHN from other respiratory and cardiac disorders by demonstrating the supra-systemic pulmonary vascular pressures.

Animal research has shown a possible therapeutic effect of BNP in PPHN. Isolated vessel studies in fetal lambs with PPHN by induced ductal ligation found an abundance of NPR-A. When exposed to BNP these pulmonary arteries and veins relaxed but the responses were significantly lower than in controls.[48] Research is underway examining the therapeutic effect of recombinant human BNP on neonates with resistant PPHN unresponsive to nitric oxide.[49]

BNP can aid in the diagnosis of PPHN. In a study of 47 term neonates, Reynolds *et al* showed significantly higher BNP levels in neonates with a diagnosis of PPHN by echocardiography than in neonates with other respiratory diseases and controls in room air. BNP levels remained elevated compared with the other two groups for the first four days and correlated well with the pressure gradient across the tricuspid valve ($r^2 = 0.83$).[8] In this study, BNP levels greater than 850 pg/ml were found only in neonates with PPHN.

BNP AND NTpBNP AS MARKERS OF LEFT VENTRICULAR FUNCTION IN PRETERM NEONATES

BNP and NTpBNP have been shown to be an invaluable adjunct to echocardiography when assessing ventricular performance in infants and children.[22 23] This benefit will have obvious advantages in neonatal intensive care. Cardiology-provided echocardiography is not routinely available in this setting to assess cardiac performance and a biochemical surrogate would be useful.

One study found no correlation between BNP and shortening fraction or blood pressure in preterm neonates.[43] However, shortening fraction is an unreliable measure of systolic left ventricular function in the first few days of life. It is measured following M-mode echocardiography of the long parasternal view of the left ventricle. The calculation is based on the difference between left ventricular end-diastolic and end-systolic diameters. High right ventricular pressures impair the movement of the ventricular septal wall. Therefore, shortening fraction does not correlate with left ventricular output, one of the major determinants of systemic perfusion in neonates. Correlating BNP and NTpBNP with left ventricular output (measured by echocardiography) may yield much more information about cardiac performance and provide a non-invasive method of assessing systemic perfusion.

Correlating BNP and NTpBNP with left and right ventricular diastolic function may provide more valuable information. A degree of diastolic dysfunction occurs in all neonates, and if severe may worsen respiratory disease and contribute to heart failure. Echocardiographic parameters have been established to assess progression through neonatal life. Linking BNP or NTpBNP may provide a simple screening test to assess the resolution of such dysfunction, especially after ductal closure, a major determinant of BNP levels. Its value could lie in differentiating cardiac from non-cardiac causes of reventilation of preterm neonates, as has been shown in children.[25 50]

BNP AND NTpBNP AS A MARKER OF NEONATAL SEPSIS

In animal models, plasma BNP levels have been shown to rise with induced endotoxaemia, and the proinflammatory cytokine interleukin-6 has been linked with BNP production. Therefore, the rise in BNP may not be solely due to ventricular overloading. In neonatal rat cardiac myocytes, transcriptional activation of the BNP gene was initiated by lipopolysaccharide (LPS), suggesting that elevated BNP levels under endotoxaemic conditions are partially mediated by LPS.[14] In patients with severe sepsis or septic shock, BNP and NTpBNP levels are highly elevated[51] and, despite significant haemodynamic differences, comparable with those found in adults with acute heart failure. It remains to be determined how elevation in natriuretic peptide levels is linked with inflammation and sepsis-associated myocardial dysfunction.[52] BNP has also been shown to have prognostic value in these patients, with levels greater than 650 pg/ml highly predictive of death.[53] NTpBNP may also serve as a useful laboratory marker predicting survival in patients with severe sepsis,[54] and it seems to be an early predictor of myocardial dysfunction in patients with septic shock.[55] In a study comparing children with sepsis and those with acute left ventricular dysfunction NTpBNP levels were higher in the latter group. However, there was a significant overlap in NTpBNP levels between the groups possibly precluding its use as a sole means to differentiate between these conditions. A cardiac aetiology may be suspected if NTpBNP levels are excessively elevated and associated with acute haemodynamic deterioration in infants and children.[56] BNP and probably NTpBNP may serve as a marker of cardiac dysfunction associated with sepsis in preterm neonates and be a useful adjunct in the diagnosis of sepsis. This possible association is currently being investigated at our centre.

CONCLUSIONS

BNP and NTpBNP have major diagnostic roles in the adult population and their role as therapeutic agents is emerging. In children, BNP and NTpBNP serve as indicators of cardiac disease and may be used to monitor response to treatment. The potential benefit of these natriuretic peptides in neonatology is immense. More studies are needed to explore the possible roles of BNP/NTpBNP in the management of sepsis and monitoring of cardiac performance. These two possible confounding factors limit their reliability in the diagnosis of PDA and its response to treatment.

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IMAGES IN NEONATAL MEDICINE

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Unusual presentation of neonatal haemophilia A

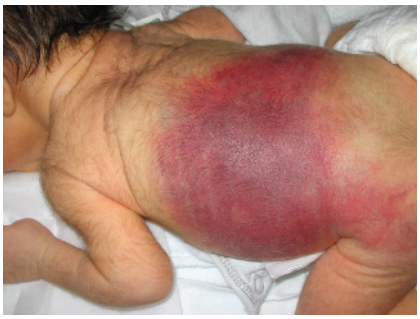

Figure 1 Widespread purple discoloration in a baby with severe haemophilia A. Parental/guardian informed consent was obtained for publication of this figure.

A second male twin was born at 36 weeks' gestation by emergency caesarian section owing to failure to progress following spontaneous onset of labour. He was difficult to deliver because of a transverse lie. He developed respiratory distress shortly after birth, requiring oxygen and antibiotics, and became lethargic, hypothermic (temperature 36.1°C) and tachycardic (174 beats/min) at 48 h of age. A large purple lesion was noted on his back (fig 1). His activated partial thromboplastin time was 186 s, reducing to 30.3 s with a 50% mix of normal plasma. Factor studies confirmed severe haemophilia A with a factor VIII:c level of <0.05 IU/ml. Haemoglobin dropped from 196 g/l to 97 g/l 48 h after birth. He required transfusion, factor VIII and phototherapy for jaundice. Cranial and abdominal ultrasound scans excluded other haemorrhages. His twin brother remained well, but screening revealed he was also affected.

In the absence of a family history, diagnosis of factor VIII deficiency is usually made following a bleeding episode, 18–54% of which occur within the first month of life.[1–3] Bleeding sites include cephalohaematomas (particularly after ventouse deliveries), puncture sites from venesection or intramuscular drug administration, after circumcision, umbilical stump bleeding, intracranial haemorrhages and bleeds into the gastrointestinal tract or other major organs.[1–5] Massive intradermal haemorrhage in the immediate newborn period has not been previously reported, although extensive bruises are a common method of presentation in older children. We assume this was related to the baby's difficult extraction at caesarean section.

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