Early Human Development xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Cardiac biomarkers and haemodynamically significant patent ductus arteriosus in preterm infants

Dany E. Weisz [a,b], Patrick J. McNamara [b,c,d], Afif El-Khuffash [e,f,*]

[a] Department of Newborn and Developmental Paediatrics, Sunnybrook Health Sciences Centre, Toronto, Canada
[b] Department of Paediatrics, University of Toronto, Toronto, Canada
[c] Department of Physiology, University of Toronto, Toronto, Ontario, Canada
[d] Physiology and Experimental Medicine Program, SickKids Research Institute, Toronto, Canada
[e] Department of Neonatology, The Rotunda Hospital, Dublin, Ireland
[f] School of Medicine (Department of Paediatrics), Royal College of Surgeons in Ireland, Dublin, Ireland

ARTICLE INFO

Available online xxxx

Keywords:
Biomarkers
Natriuretic peptides
BNP
PDA
Preterm Infants

ABSTRACT

Accurately defining haemodynamically significant patent ductus arteriosus (PDA) in preterm infants who are at risk of PDA related morbidities are active areas of neonatal research. Natriuretic peptides are cardiac hormones that respond to volume and pressure loading, with elevated plasma levels found in infants with PDA. In the preterm neonatal setting, studies to date have predominantly investigated the ability of these biomarkers to discriminate between infants with and without a PDA at various postnatal ages. Their clinical utility has therefore been exclusively evaluated as a method of triaging cases of suspected hsPDA to decrease the need for echocardiograms, and to monitor treatment response. Biomarkers are yet to be robustly investigated for their ability to predict important PDA associated morbidities. In this review, we examine the most recent literature to date on the use of biomarkers in the management of PDA.

1. Introduction

There has been an increasing interest to more accurately define and characterise preterm infants with a patent ductus arteriosus (PDA) who eventually develop PDA related morbidities, including death, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), and chronic lung disease (CLD). Ideally, predicting PDA associated morbidities should occur during the early neonatal course (within the first 48–72 h). This may facilitate early targeted treatment, limiting the number of infants exposed to potentially harmful medication, and maximising the benefit to those treated. PDA related morbidities are more likely to occur with a haemodynamically significant PDA (hsPDA). Although the definition of a hsPDA remains variable and lacks consensus, it is generally attributed to PDAs associated with echocardiography and clinical evidence of systemic hypoperfusion, and pulmonary over-circulation. The magnitude of the shunt across the PDA determines the severity of those markers. Recent evidence suggests that no single echocardiography or clinical marker accurately predicts PDA related morbidities. PDA diameter, the most commonly used marker to determine treatment, is poorly predictive of relevant clinical outcomes (IVH, NEC, CLD and Death) [1,2]. A combination of clinical and echocardiography appraisal of a PDA may have better predictive ability than an isolated single marker [2,3]. Although this is an area of active research, this approach to PDA treatment has not been systematically tested in randomised control trials. An increasing body of literature has examined the utility of cardiac biomarkers to diagnose, stage, and predict treatment response to a PDA. Biomarkers may be an important addition to disease staging of a PDA that may be useful in characterising shunt severity, determining which PDAs warrant treatment, and predicting PDA related morbidities. In this review, we examine the most recent literature to date on the use of biomarkers in the management of PDA.

1.1. Cardiac Biomarkers: natriuretic peptides

Natriuretic peptides are cardiac hormones that rapidly respond to volume and pressure overload; plasma levels are elevated in patients with left and right heart failure. Atrial natriuretic peptides (ANPs), brain natriuretic peptides (BNPs) and their respective inactive peptide fragments (mid-regional pro-ANP [MR-proANP] and N-terminal pro-BNP [NTpBNP]) have been evaluated in the preterm neonatal population. MR-proANP is released by atrial myocytes in response to elevated transmural atrial pressures and is present in the myocardium of fetuses and neonates [4]. It is simultaneously secreted in equimolar amounts as the biologically active ANP, though is present in more stable levels due to a longer half-life [5]. Myocytes in the cardiac ventricles secrete pro-BNP in response to pressure and volume loading, which is subsequently cleaved into the biologically active BNP and the inactive fragment

* Corresponding author at: The Rotunda Hospital, Dublin, Ireland.
E-mail address: afifelkhuffash@rcsi.ie (A. El-Khuffash).

http://dx.doi.org/10.1016/j.earlhumdev.2016.12.007
0378-3782/

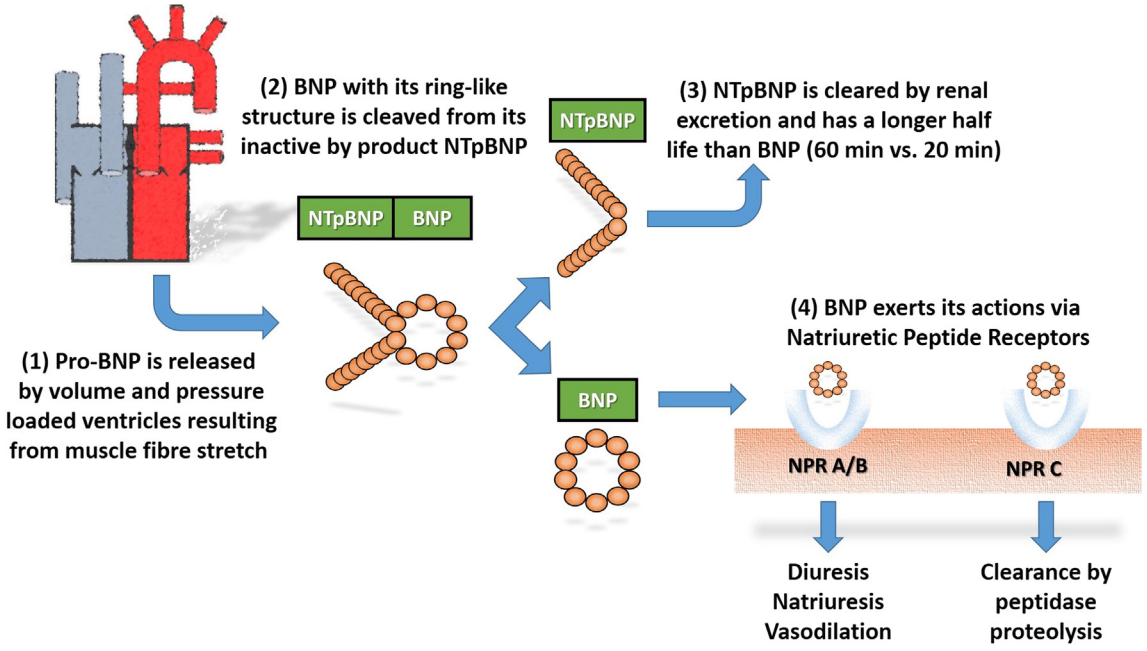

Fig. 1. Pro-B type Natriuretic Peptide secretion, mode of action and clearance.

NTpBNP [6]. BNP derives its name from being first isolated in the porcine brain. ANP and BNP inhibit the renin-angiotensin-aldosterone axis and sympathetic nervous system, vasodilate the systemic and pulmonary circulations, inhibit vasopressin release, and promote natriuresis and diuresis (Fig. 1).

2. Natural history and physiological influences of natriuretic peptides

Natriuretic peptides do not appear to cross the placenta and therefore variation in levels are likely due to intrinsic fetal or neonatal factors [7]. Natriuretic peptides are cleared by the kidneys and are therefore elevated in patients with renal dysfunction. Normative data for healthy infants have been reported, with levels inversely correlated with advancing gestational age (Table 1). In both well preterm and term infants, BNP levels rise after birth, peak at 24–48 h and then decline [8–10]. In healthy term infants, there is no correlation between BNP concentrations and echocardiography indices of myocardial function or volume loading, mode of delivery, birthweight or gender in the first weeks of life [11]. However, by day 30 of life, BNP concentrations have moderate correlation with echocardiography indices of left ventricular dimension, mass and filling, but not ventricular function [11].

Compared with term infants, BNP and NTpBNP concentrations are higher in preterm infants, possibly due to the inability of the immature myocardium to overcome the increased left and right ventricular afterload (respectively due to umbilical cord clamping and respiratory distress syndrome). Early BNP concentrations in preterm infants are uninfluenced by maternal hypertension or premature rupture of membranes. As with term infants, day 3 plasma BNP concentrations do not correlate with echocardiography parameters in preterm infants without

Table 1
Reference ranges for plasma BNP, NTpBNP and cardiac troponin T in term and preterm infants without PDA.

Day of life	Plasma MR-proANP (pmol/L)	Plasma BNP (pg/mL)			Plasma NTpBNP (fmol/mL or pmol/L)		Urine NTpBNP (fmol/mL or pmol/L)
	Moderate/extremely preterm infants	Term infants[c]	Moderate/late preterm infants[c]	Moderate/extremely preterm infants[d]	Term infants[e]	Moderate/extremely preterm infants[f]	Moderate/extremely preterm infants[g]
Umbilical cord/birth	535 [95% range, 265–1360][a]	10.6 [7.5–13.9]	31 [7.2–98.6]	–	222 [58–779]	–	–
Day 1		–	84.4 [30.6–471.5]	362 [94–780]	641 [254–1272]	1435 [894–2550]	600 [480–2288]
Days 2–3	865 [445–1569][b]	57.2 [22.8–84.1]	35.7 [14.2–119.7]	196 [115–1146]	–	1127 [509–2884]	600 [566–1802]
Days 6–8	1481 [750–1842][b]	–	–	70 [23–227]	–	–	600 [273–864]
Day 30		8.7 [5.7–12]	12.7 [5–16.2]	43 [12–158]	–	–	–

Data presented as median [interquartile range (IQR)] unless otherwise specified.
BNP, brain natriuretic peptide; MR-proANP, mid-regional pro atrial natriuretic peptide; NTpANP, N-terminal pro-atrial natriuretic peptide; NTpBNP, N-terminal pro-brain natriuretic peptide.
[a] Data from Letzner et al. [14] Median GA 28–30 weeks. [Kryptor, Brahms Biomarkers]
[b] Data from Grass et al. [15] Median GA 28 weeks [IQR 26.9–31.3]. [Kryptor, Brahms Biomarkers]
[c] Data from Mannarino et al. [12] [Triage, Biosite]
[d] Data from da Graca et al. [13] Mean GA 27.6 weeks (±2.59). [Triage, Biosite]
[e] Data from Mir et al. [10] [Enzyme Immuno Assay, Biomedica]. Data presented as median [range].
[f] Data from El-Khuffash et al. [31] Median GA 28 weeks [IQR 26.1–29.5]. [Electro chemiluminescence immunoassay, Roche]
[g] Data from Tosse et al. [34] Median GA 28.1 weeks [range 24.1–33.0]. [Enzyme immunoassay, Biomedica Medizinprodukte GmbH & Co. KG]

Please cite this article as: D.E. Weisz, et al., Cardiac biomarkers and haemodynamically significant patent ductus arteriosus in preterm infants, Early Hum Dev (2016), http://dx.doi.org/10.1016/j.earlhumdev.2016.12.007