The Decline and Fall of the Cardiac Biomarker: A Good Indicator of Resolution of Cardiac Dysfunction following Perinatal Asphyxia

Commentary on D.C. Vijlbrief et al.: Cardiac Biomarkers as Indicators of Hemodynamic Adaptation during Postasphyxial Hypothermia Treatment (Neonatology 2012;102:243–248)

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Neonatal asphyxia induces global hypoxia-ischaemia resulting in multi-organ injury [1]. Cardiac, renal, hepatic and haematological dysfunction are well-described. Martín-Ancel et al. [2] found that 29% of neonates with perinatal asphyxia had cardiac dysfunction consistent with myocardial ischaemia.

Hypothermia is the latest treatment for neonatal brain injury following perinatal asphyxia to come into widespread use [3]. Infants with perinatal asphyxia treated with hypothermia have decreased biventricular function and coronary artery flow and significantly elevated troponin compared with normal term control infants [4]. In addition the cardiac biomarker cardiac troponin I (cTnI) and pathological cardiac lesions are significantly reduced after hypothermia treatment in hypoxic-ischaemic newborn pigs [5]. Hypothermia has a direct cardioprotective role and reduces cardiomyocyte injury after oxidative stress in animal models [6]. However, the effect of hypothermia on cardiac biomarkers has not been extensively investigated in human newborns.

The paper 'Cardiac biomarkers as indicators of hemodynamic adaptation during postasphyxial hypothermia treatment' by Vijlbrief et al. [7] reports an observational cohort study of infants treated with mild hypothermia following perinatal asphyxia. They investigated whether hypothermia exerts a beneficial effect on the heart after

perinatal asphyxia using the cardiac biomarkers cTnI and brain natriuretic peptide (BNP). Troponin T and I are sensitive markers of myocardial injury following a perinatal hypoxic-ischaemia insult. BNP is a marker of ventricular wall stress secondary to myocardial dysfunction [8]. cTnI and BNP were collected before the start of hypothermia, at 24 and 48 h after birth, and after rewarming. BNP was significantly lower in the infants who underwent hypothermia compared with historical controls with perinatal asphyxia but not treated with hypothermia. The authors did not see a difference in troponin levels in the 2 groups which normalised in both groups by 84 h of age. This study differed from other studies of neonatal cardiac dysfunction following perinatal asphyxia and hypothermia as comparison was made with historical controls with perinatal asphyxia rather than normal healthy controls. This may explain why the authors found decreased BNP and no difference in troponin in infants treated with hypothermia. This study is interesting as it shows that although following perinatal asphyxia troponin levels are very elevated they decline to normal levels in both groups by day 4 of life, which may indicate complete resolution of cardiac dysfunction.

Cardiac troponin T, cTnI and BNP are well-described markers of myocardial ischaemia and cardiac failure in adults, children and neonates [9]. BNP is released in re-

sponse to volume and pressure loading and ventricular stress. Cardiac troponin I is released from myocytes in both reversible and irreversible myocardial injury. The changes in myocyte membrane permeability resulting from the injury could be enough for the release of cardiac troponins from the free cytosolic pool of myocytes without permanent structural damage. Both BNP and troponin are elevated in preterm infants with a significant patent ductus arteriosus and decrease with closure of the ductus [10, 11] and both have been used to evaluate the response to treatment of congenital heart disease [12]. BNP is elevated in persistent pulmonary hypertension of the newborn and correlates well with the pressure gradient across the tricuspid valve [13] and therefore may be a useful marker in infants with persistent pulmonary hypertension of the newborn following perinatal asphyxia. Cord blood BNP also significantly elevated in infants requiring inotropes with a range of diagnoses including a subgroup with perinatal asphyxia [14].

The paucity of echocardiography in many neonatal centres increases the importance of surrogate markers of cardiac dysfunction such as BNP, NTproBNP and troponin. Serial levels of these cardiac biomarkers could be used to evaluate the severity of cardiac compromise and responses to therapy such as inotropes without the need

for constant echocardiography on a 24-hourly basis. In addition their potential as markers of longer-term cardiac function requires evaluation in conjunction with echocardiography. Point of care sampling of BNP and troponin would simplify their use in the neonatal intensive care unit as cardiac biomarkers and has been validated for this purpose [15]. Elevated troponin, NTpBNP (inactive by-product of the cleavage of ProBNP to BNP) at 48 h identifies preterm infants with a patent ductus arteriosus at greatest risk of death or poor 2-year neurodevelopmental outcome [11]. Therefore, although initial troponin levels normalize in many infants, the maximum troponin level may indicate the degree of perinatal asphyxia. Although evidence of cardiac dysfunction and injury is well-described following perinatal asphyxia, there is a need for cardiovascular as well as neurodevelopmental follow-up studies to see if this is a sustained effect that may have implications in later childhood or adulthood.

The advent of newer therapies such as xenon in combination with hypothermia may also improve cardiovascular outcomes as demonstrated in a neonatal piglet model of hypoxia-ischaemia [16]. Incorporating cardiac biomarkers in future neonatal clinical cardiovascular research may facilitate their use in routine clinical practice.

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