INTRODUCTION

Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation and can present as late as 4-6 weeks postpartum. It is clinically defined by hypertension and proteinuria, with or without pathologic edema ***(Vatten and Skjaerven, 2004)***.

Impaired uteroplacental blood flow in pre-eclamptic pregnancies may result in the development of functional and structural anomalies in many fetal organs due to intrauterine hypoxia. Fetal myocardium is also affected. Various clinical manifestations ranging from mild cardiac failure due to dysrhythmia to cardiovascular collapse may emerge as a consequence of perinatal asphyxia ***(Karadeniz et al., 2010).***

Troponin is an inhibitory protein complex forming part of the contractile apparatus of all striated muscles, including the heart. Specific forms of the three troponin subunits T, C, and I exist in different muscle types ***(Hetland and Dickstein, 1998; Clark et al., 2004).***

Cardiac troponin T (cTnT) structure is unique to the myocardium which allows assessment of cardiac injury even in the presence of skeletal one ***(Adamcova et al., 2000).***

Although wide consensus has been established on the clinical utility of troponins in adults with acute coronary syndrome, troponins have not been used routinely in neonates ***(Trevisanuto et al., 2006).***

AIM OF THE WORK

The aim of this study was to determine cord blood cTnT levels in preterm neonates of preeclamptic mothers and to correlate these levels with their cardiac functions measured by echocardiography.

CARDIAC TROPONINS

Cardiac troponins are protein components of the tropnin-tropomyosin complex in myocardium. Since troponins do not occur in extracellular space, their appearance in serum is sensitive and specific marker of myocardium damage ***(Tarkowska and Furmaga-Jabłońska, 2012).***

Cardiac troponins have a major role in screening and diagnosis of myocardial ischaemia in adults and children. Their introduction has redefined the diagnosis of myocardial infarction in adults and provided valuable prognostic information. In the paediatric population, troponins show a good correlation with the extent of myocardial damage following cardiac surgery and cardiotoxic medication, and can be used as predictors of subsequent cardiac recovery and mortality ***(El-Khuffash et al., 2008).***

Troponin is a family of three proteins that act together in inhibiting the binding of myosin to actin strands. This family compromises three troponin structures T, C and I. These form a complex with an inhibitory part (I) that binds to the actin, blocking the active binding site that the myosin molecule needs. The T structure binds to tropomyosin (a long protein which also blocks the myosin binding by coiling with the actin double helix on top of its binding sites). Troponin C (TnC) joins the two sides of the complex and, using its EF hand structure performs a conformal change in the molecules moving

the tropomyosin and the I structure away from myosin's binding site. This conformal change is initiated via a binding of Ca2+ onto the TnC structure ***(Lewit-Bentley and Rety, 2000).*** This action is illustrated in figure (1).

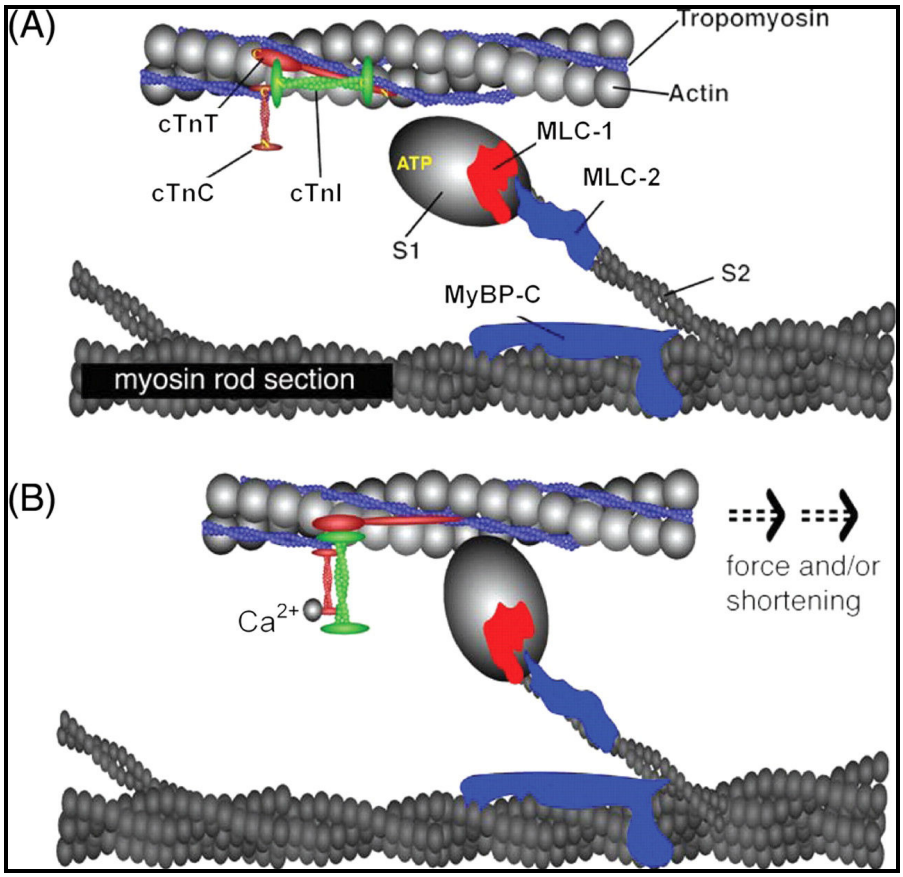

Figure (1): Diagram showing basic structure of the troponin complex and the binding of myosin after the Ca2+ induced conformal change ***(Hamdani et al., 2007).***

Sensitivity of both cTnT and cTnI in the diagnosis of myocardial damage is clinically almost equal. They differ in

intracellular compartments, biological half-life, and molecular weight ***(Adamcova, 2003).***

TnC exists in highly homogenous isoforms in cardiac and skeletal musles, and are therefore not used in assays for the diagnosis of cardiac injury **(*Mohammed and Januzzi, 2010*).**

Different forms of TnT and TnI are found in cardiac, fast twitch and slow twitch skeletal muscles. Each muscle-specific troponin type is encoded by separate genes ***(Gaze and Collinson, 2008).***

Troponins appear in blood in 2 to 4 hours after insult, peak in about 12 h and then remain elevated for 7–10 days ***(Tarkowska and Furmaga-Jabłońska, 2012).***

Cardiac troponins I or T are the preferred and recommended biomarkers of coronary acute syndromes ***(Wu et al., 1999; Thygesen et al., 2007; Thygesen et al., 2012)*** due to their high myocardial tissue specificity and high clinical sensitivity. Detection of a rise and/or fall of the troponin measurements, coupled with clinical symptoms and/or electrocardiogram is necessary to diagnose acute myocardial infarction ***(Jaffe, 2006).*** Blood samples for the measurement of troponin should be drawn for biomarker testing at hospital presentation followed by sampling at 6–9 h, although the new high sensitivity assays make possible the measurement on

admission and 3–6 h later, shortening the turnaround time ***(Thygesen et al., 2012).***

Serum cardiac troponin T (cTnT) is a marker of cardiac injury and mortality in adults and is a good marker of myocardial injury in perinatally asphyxiated neonates ***(El-Khuffash et al., 2008).***

The decision for including cardiac troponins (cTn) in the diagnostic pathway was made because of the high sensitivity of cTn for detection of even small amounts of myocardial necrosis. An elevation of cTn indicates the presence of, but not the underlying reason for, myocardial injury. Hence, besides acute myocardial infarction (AMI), there is a myriad of potential diseases with troponin release, including acute pulmonary embolism, heart failure, myocarditis, and end stage renal disease. But regardless of what the release mechanism into the blood from cardiac myocytes is, elevated cTnT and cTnI almost always imply a poor prognosis ***(Korff et al., 2006).***

Measuring cardiac troponin for detection of myocardial infarction

The criteria of the universal definition of AMI is a rising and/or falling pattern of cTn concentrations with at least one value above the 99th percentile limit of the reference value distribution in the setting of a patient with clinical features of myocardial ischaemia ***(Thygesen et al., 2007).*** The latter is

indicated by symptoms of ischaemia, ECG changes indicative of new ischaemia, development of pathological Q-waves, or imaging evidence of the new loss of viable myocardium or new regional wall motion abnormalities ***(Thygesen et al., 2007).*** Serial measurements of cTn are necessary when cTn concentration is not elevated on admission as cTn values may not appear in blood within the first hours after myocardial injury. As the timing of symptoms may not be totally reliable, cTn must be measured on admission and 6 – 9 h later. In patients with an intermediate or high clinical index of suspicion who remain cTn negative, and in those with plausible recurrence of ischaemic symptoms, repeat testing at 12 – 24 h should be considered to increase diagnostic sensitivity. Given the rapid positivity of contemporary assays, some have advocated a sample at 3 h after admission as well since upwards of 80% of AMI patients will have elevations by that time ***(MacRae et al., 2006).*** Elevated cTn values in patients with acute ischaemic presentations are related to more extensive coronary artery disease (CAD), pro-coagulant activity, and lower coronary perfusion. As such, they mark patients at higher risk for the development of cardiac events during short- and long-term follow-up ***(Thygesen et al., 2012).***

Other causes of cardiac troponin release:

Table (1) summarizes other causes of myocardial damage, which can be separated into causes of secondary myocardial ischaemia (AMI type 2), diseases not associated with myocardial ischaemia, and conditions where the exact mechanisms are uncertain or multifactorial. Elevations of cTn, related to putative supply – demand abnormalities (ischaemia due to increased myocardial work in the absence of a significant structural or functional abnormality in a coronary artery), should be labelled as cardiac damage but not necessarily AMI even if there are ST and/or T wave changes. Other frequent mechanisms of troponin increases not related to ischaemia include myocardial damage due to inflammatory processes or toxic agents or trauma ***(Blich et al., 2008).***

Patients with elevated cTn values should be followed closely since these elevations in almost all situations are associated with an adverse prognosis ***(Thygesen et al., 2010).*** Some of these patients if they manifest acute presentations may have a rising and/or falling pattern of cTn values. Patients without a changing pattern (see caveats above in regard to the timing of the evaluation) should not be diagnosed as having AMI or other acute reasons for the elevation. Some patients with stable coronary artery disease (CAD), chronic renal failure, chronic heart failure, and severe left ventricular

hypertrophy can have chronic elevations of cTn which may or may not change markedly over the short term ***(Katz et al., 2005; Wallace et al., 2006; Zethelius et al., 2006; Daniels et al., 2008).*** These individuals including those with values above the 99th percentile limit should not be diagnosed as having AMI or other acute aetiologies for the cTn elevations in the absence of significant changes in values over time. However, the higher the cTn values, the higher is the likelihood of an AMI ***(Thygesen et al., 2010).***

Elevated cardiac troponin in heart failure:

Patients admitted with acute onset or worsening of heart failure require particular attention. Often the substrate for heart failure is CAD. However, even individuals with dilated cardiomyopathy can have elevated cTn values with or without imaging evidence of cardiac injury. Some of these elevations could be related to subendocardial supply – demand abnormalities since wall stress is an important determinant of subendocardial blood flow. It may be that some of these elevations are related to coronary endothelial dysfunction which is known to occur in heart failure patients ***(Katz et al., 2005)***, but cardiomyocyte injury may also be due to acute left ventricular stretch which may cause proteolysis and release of cTn ***(Feng et al., 2007).***

Elevated cardiac troponin in renal disease:

Patients with severe or end-stage renal failure have often elevations of cTns and especially of cTnT. However, no satisfying generally accepted explanation of that has been found yet despite evidence of diffuse myocardial injury ***(Khan et al., 2005; Apple et al., 2002; Sharma et al., 2006).*** The mechanisms involved may be similar to those observed in heart failure patients or could be related to renal failure metabolic milieu which may cause skeletal muscle myopathies as well ***(Thygesen et al., 2010).*** Thus, if cTnI and cTnT increase in skeletal myopathy, cardiac involvement must be suspected. However, these individuals usually have chronic elevations and should only be diagnosed as having AMI when they present with compatible symptoms, ECG or imaging findings, and a rising pattern of cTn values. Regardless of the mechanisms, the risk of death in end-stage renal failure patients increases directly with the measured cTnT concentration ***(Khan et al., 2005).***

Table (1): Elevations of cardiac troponin in the absence of overt ischaemic heart disease

Damage related to secondary myocardial ischaemia (MI type 2)
Tachy- or bradyarrhythmias
Aortic dissection and severe aortic valve disease
Hypo- or hypertension, e.g. haemorrhagic shock, hypertensive emergency
Acute and chronic heart failure without significant concomitant coronary artery disease (CAD)
Hypertrophic cardiomyopathy
Coronary vasculitis, e.g. systemic lupus erythematosus, Kawasaki syndrome
Coronary endothelial dysfunction without significant CAD, e.g. cocaine abuse
Damage not related to myocardial ischaemia
Cardiac contusion
Cardiac incisions with surgery
Radiofrequency or cryoablation therapy
Rhabdomyolysis with cardiac involvement
Myocarditis
Cardiotoxic agents, e.g. anthracyclines, herceptin, carbon monoxide poisoning
Severe burns affecting > 30% of body surface
Indeterminant or multifactorial group
Apical ballooning syndrome
Severe pulmonary embolism or pulmonary hypertension
Peripartum cardiomyopathy
Renal failure
Severe acute neurological diseases, e.g. stroke, trauma
Infiltrative diseases, e.g. amyloidosis, sarcoidosis
Extreme exertion
Sepsis
Acute respiratory failure
Frequent defibrillator shocks

(Thygesen et al., 2010)

Role of cardiac troponins in neonatal diseases

Growth restriction and antenatal stress

Placental dysfunction leading to growth restriction and preeclampsia is a common and serious complication during pregnancy. Placental dysfunction leads to hypoxemia and nutritional deficiency with inevitable effects on myocytes and cardiac function ***(Girsen et al., 2007; Crispi et al., 2008)***. Elevated levels of cTnT were found in infants born to mothers who experienced preeclampsia, thereby associating maternal disease to neonatal myocyte compromise ***(Karadeniz et al., 2010).*** Makikallio *et al.* found that cTnT levels were elevated in infants born after severe placental insufficiency, although other studies failed to show an increase in cTnI levels during intrauterine growth restriction ***(Makikallio et al., 2000; Crispi et al., 2008).***

Perinatal asphyxia

Troponins appear in the blood 2-4 h after perinatal asphyxia and consequent myocardial compromise, and remain detectable for up to 21 days ***(Bertinchant et al., 1996).*** Much research has been done to evaluate the predictive value of cord blood cardiac troponins ***(Turker et al., 2004; Trevisanuto et al., 2006).*** Moller et al. showed that cTnT had a high positive predictive value in the postnatal diagnosis of perinatal asphyxia ***(Moller et al., 1998).*** Szymankiewicz et al. determined cTnT levels at 12 and 24 h after birth in infants who had experienced

asphyxia and those who had not. The authors of that study found cTnT to be the most useful tool for assessing myocardial injury. In their study, echocardiography appeared to be of less value, apart from its help in diagnosing tricuspid insufficiency, reported earlier as being more common in newborns who had experienced asphyxia ***(Szymankiewicz et al., 2005).*** However, Costa et al. did report such a relationship between higher cTnT levels and echocardiographic signs of myocardial compromise in infants who had experienced asphyxia. In newborns with echocardiographic signs of myocardial compromise (diminished left-ventricular output and stroke volume), cTnT levels were found to be more elevated ***(Costa et al., 2007).*** The levels of cTnT and cTnI are related to the severity of perinatal hypoxia-ischemia ***(Gunes et al., 2005; Shastri et al., 2012).***

Impaired uteroplacental blood flow in pre-eclamptic pregnancies may result in the development of functional and structural anomalies in many fetal organs due to intrauterine hypoxia. Fetal myocardium is also affected. Various clinical manifestations ranging from mild cardiac failure due to dysrhythmia to cardiovascular collapse may emerge as a consequence of perinatal asphyxia. Cardiac troponin T (cTnT), a cardiac structural protein, is regarded as a highly specific and sensitive marker of myocardial damage ***(Karadeniz et al., 2010).***

Increased levels of serum cTnT are reported to indicate myocardial damage in babies of mild pre-eclamptic mothers ***(Karadeniz et al., 2010).***

Persistent pulmonary hypertension

Persistent pulmonary hypertension of the neonate (PPHN) is a severe disease seen mostly in term infants. Because PPHN is usually associated with conditions affecting pulmonary function (sepsis, meconium aspiration, asphyxia), it is often difficult to arrive at an early diagnosis of PPHN, especially when echocardiographic evaluation is not available ***(Bernus et al., 2009).*** Torbicki et al. studied cTnT as an independent marker of increased mortality risk in adult patients with chronic pre-capillary pulmonary hypertension. The results suggested a relationship between right-ventricular dysfunction and cTnI levels. However, similar studies have not been carried out in infants ***(Torbicki et al., 2003).***

Sepsis

Clark et al. found that the cTnT levels were significantly higher in sick infants than in healthy ones. The use of inotropic support and oxygen requirement were independently associated with higher cTnT levels ***(Lodha et al., 2009).***

PREMATURITY

Preterm birth is a major challenge in the perinatal health care ***(Tucker and McGuire, 2004).*** Despite advances in obstetric care, the rate of prematurity has not changed substantially over the past 40 years and actually have been increased slightly in the recent decades. Prematurity remains a leading cause of neonatal morbidity and mortality worldwide, accounting for 60% to 80% of deaths of infants without congenital anomalies ***(Ramsey and Goldenberg, 2006).***

The preterm neonate is the one born after the 28th week of pregnancy (the fetus is viable) and before the 37th week from the date of the last menstrual cycle irrespective to his weight ***(Dammann et al., 2006).***

Preterm labor is defined as the onset of regular uterine contractions producing cervical change before 37 weeks of gestation, indicating the risk of preterm delivery ***(Parer, 2003).***

Measures of live-born infant size include low birth weight (LBW) (infants weighing less than 2500 g) and two subgroups of LBW, moderately low birth weight (infants weighing between 1500 and 2499 g) , very low birth weight (infants weighing less than 1500 g),and Extremely low birth weight (ELBW) infants weighing less than 1000g ***(Walsh and Fanaroff, 2006).***