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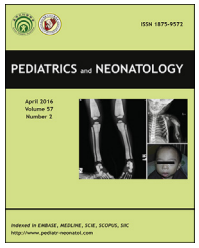

ORIGINAL ARTICLE

Myocardial Injury Biomarkers in Newborns with Congenital Heart Disease

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Key Words
cardiac biomarkers;
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echocardiography;
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Background: Troponin I, myoglobin, and creatine kinase-MB mass (CK-MB) are biomarkers of cardiomyocyte injury widely used in the management of adult patients. The role of these biomarkers in newborns is still not established. The purpose of this study was to evaluate the value of cardiac injury biomarkers in newborns with congenital heart disease.
Methods: From August 2012 to January 2014, 34 newborns with a prenatal diagnosis of congenital heart disease were admitted consecutively to a neonatal intensive care unit. As controls, 20 healthy newborns were recruited. Plasma levels of cardiac biomarkers (troponin I, myoglobin, and CK-MB) were evaluated, and echocardiography was performed to evaluate cardiac function on D 1. Patients were followed during the first 28 days of life and, according to outcome, categorized as surgical or conservative treatment group.
Results: Median (P25–75) levels of CK-MB were higher in patients who underwent cardiac surgery in the neonatal period [7.35 (4.90–13.40) ng/mL] than in patients who were discharged home without surgery [4.2 (2.60–5.90) ng/mL; $p = 0.032$]. A CK-MB cutoff of $\geq$ 4.6 ng/mL

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showed sensitivity of 87.5% and specificity of 63.6%. Troponin I and myoglobin levels were not significantly different between conservative and surgical treatment groups. CK-MB levels correlated with the tissue Doppler image of the mitral valve lateral annulus peak early/late diastolic velocity ratio ($\rho = -0.480$, $p = 0.018$).
Conclusion: CK-MB levels during the first hours of life were higher in newborns that needed neonatal cardiac surgery, and these levels may be an indicator of myocardial diastolic function.
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1. Introduction

Creatine kinase-MB mass (CK-MB), myoglobin, and cardiac troponins I and T are cardiac injury biomarkers widely used in the management of adult patients.[1,2] Interest in these cardiac biomarkers in the management of children with congenital heart disease (CHD) has increased; however, there are no current guidelines for their routine use. Reference values for CK-MB and cardiac troponins T and I in healthy neonates have been published.[3–6] CK-MB levels were elevated in newborns after perinatal and neonatal hypoxia–ischemia, but this elevation was not specific enough to be of clinical value.[7] Myoglobin is a cytoplasmic protein in cardiac and skeletal muscle, and it passes rapidly into circulation after damage to the myocytes.[6,8] Troponin I was found to be a very sensitive and specific marker of cardiac injury.[2,4,9] Troponin I has been used to detect myocardial compromise in newborns with hypoxia and asphyxia,[10,11] and it was shown to be useful for monitoring myocardial injury in infants of diabetic mothers: an elevated troponin I in infants of diabetic mothers with respiratory distress was a good predictor of hypertrophic cardiomyopathy and/or left ventricular dysfunction.[12] Troponin I has also been studied in children with left-to-right shunt-induced myocardial injury.[13,14] Further research is necessary before cardiac injury biomarkers can be used in clinical practice in this age group.[15,16]

Our hypothesis was that plasma cardiac injury biomarkers might be increased in newborns with CHD, correlated with echocardiographic markers of biventricular function, and useful in the management of these patients.

2. Methods

2.1. Study design and patient population

This is a prospective study of 34 consecutive newborns with a prenatal diagnosis of CHD, who were admitted at the Neonatal Intensive Care Unit of S. João Hospital Center, Porto, Portugal, between August 2012 and January 2014. Additionally, 20 healthy newborns delivered in the same hospital were recruited as controls. Plasma biomarkers were evaluated on Day 1 (with umbilical cord blood after birth or the first sample collected for clinical purposes). The umbilical cord blood was collected after birth following the standard protocol. In the few cases in which it was not possible to collect a cord sample (spasm of the cord or sample coagulation), the peripheral venous blood was collected as soon as a clinical sample for the newborn was performed (the first few hours of life).

Plasma biomarkers evaluated were troponin I, myoglobin, and CK-MB. In all control group newborns except for one, all the biomarkers were measured. In the CHD group, troponin I was available in 33, myoglobin in 26, and CK-MB in 26. The missing values were due to insufficient sample volume.

Plasma biomarkers were compared using all patients' samples and also using only cord blood samples. Troponin I, myoglobin, and CK-MB were measured by way of chemiluminescent immunoassays using an Architect i2000 automated analyzer (Abbott, Lisboa, Portugal).

CHD cases were subdivided into right ventricle pressure overload ($n = 6$), left ventricle pressure overload ($n = 5$), Ebstein disease ($n = 2$), transposition of great arteries ($n = 4$), left-to-right shunts ($n = 6$), and total pulmonary anomalous venous return ($n = 1$) groups.

The right ventricle pressure overload group included four patients with tetralogy of Fallot, one patient with double outlet right ventricle with pulmonary stenosis, and one patient with pulmonary atresia with ventricular septal defect. The left ventricle pressure overload group included two patients with coarctation of the aorta, one patient with aortic stenosis, one patient with aortic atresia with ventricular septal defect, and one patient with interruption of the aortic arch. The group of transposition of great arteries included two patients with transposition of great arteries and two patients with transposition of great arteries with ventricular septal defects. The left-to-right shunt group included three patients with atrioventricular septal defects, two patients with ventricular septal defects, and one patient with patent ductus arteriosus (PDA). Two patients were excluded because they did not have a surgical indication (supraventricular tachycardia and a small muscular ventricular septal defect).

Patients were followed during the first 28 days of life (neonatal period) and, according to the outcome, categorized as surgical or conservative treatment group.

Of the 24 patients with CHD with a surgical indication (with a type of CHD expected to require surgery at some point in life), 10 had cardiac surgery in the neonatal period: systemic to pulmonary shunts ($n = 3$), arterial switch ($n = 2$), Norwood ($n = 1$), aortic valvuloplasty ($n = 1$), pulmonary banding ($n = 1$), correction of coarctation of

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