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Highly Sensitive Cardiac Troponin-I in Congenital Heart Disease
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Cardiac troponin (cTn) is a well-known, sensitive cardiac biomarker of acute coronary syndrome and acute myocardial infarction. The cTn protein complex is immobilized on the thin filament of the contractile machinery of the cardiomyocyte. It consists of 3 distinct proteins (cTnC, cTnT, and cTnI) that are encoded by separate genes. cTnI has not been reported to be expressed outside of cardiac tissue. Fetal isoforms of cTnT exist in diseased and regenerating skeletal muscle, but the new generation cTnT assay can avoid detection of these fetal forms. Therefore, cTnI and cTnT are highly specific cardiac markers that are extremely valuable and sensitive in the diagnosis of myocardial necrosis and risk stratification.

Although it is formally stated that cTn is only released when cardiomyocytes undergo necrosis (Figure), there are a number of clinical situations where cTn is present in the circulation, without any apparent cardiac necrosis. For example, elevated cTn has been reported in association with sepsis, septic shock, and systemic inflammatory response syndrome, hypotension or hypovolemia, acute and chronic heart failure, and atrial fibrillation or other tachyarrhythmias. These clinical settings indicate that demand ischemia, which refers to a mismatch between myocardial oxygen demand and supply in the absence of flow-limiting epicardial stenosis of coronary arteries, may induce cTn elevation in the circulation. Simultaneously, myocardial oxygen delivery may be decreased by reduced coronary perfusion because of tachycardia and decreased oxygen delivery to the heart.

The cardiac troponins are predominantly myofibril bound with only approximately 5–8% of both cTnI and cTnT being unbound in the cytosol. In any cardiomyocyte injury it will be this unbound pool of cTn that is released first. In the case of demand ischemia, the elevation of cTn is relatively smaller and its half-life in the circulation is usually substantially shorter than that seen when cTn is released following myocardial infarction with frank necrosis. One possible explanation for the mechanism by which cytoplasmic molecules can be released without cellular necrosis is the formation of membranous blebs, which develop during cellular ischemia and bud off from the plasma membrane of the cell. If the ischemia is limited and re-oxygenation occurs, the blebs may be released into the circulation without rupture of the plasma membrane, resulting in a one-off release of cytoplasmic con-

Figure. Release of cardiac troponins from cardiomyocytes. Both structural troponin (myofibril bound) and cytosolic troponin (free) are released into the blood with necrosis. Only cytosolic troponin may be released without necrosis.

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tents, including macromolecules. Evidence from cardiac studies has been presented to support the presence of membranous blebs in cardiomyocytes, enabling cTnI to be released from cardiac cells by ischemia alone, without necrosis.

In this issue of the Journal, Sugimoto et al report that the serum cTnI levels in children with atrial and ventricular septal defects (ASD, VSD) were significantly higher than those in healthy children. A previous study using an old-generation cTnI assay reported that preoperative cTnI concentrations in patients with ASD and VSD were within normal limits and were frequently less than the level of detection for the assay (0.4 ng/ml). In the present study, Sugimoto et al measured the serum cTnI levels using a new generation highly sensitive cTnI assay (the lower limit of detection 0.002 ng/ml) and found the significant difference between the patients and healthy children. Their findings indicate that significant volume and pressure overload at the ventricles because of congenital left-to-right shunt may cause myocardial damage. In these congenital cases, myocardial demand ischemia may be induced by ventricular enlargement, wall hypertrophy, elevation of end-diastolic pressure, tachycardia and several humoral factors associated with heart failure, such as cytokines and catecholamines. The question is whether the myocardial injury in children with ASD or VSD is reversible or causes significant irreversible myocardial remodeling. The authors mentioned that patients with VSD/PH may have irreversible myocardial injury and remodeling. There is no apparent evidence of irreversible functional or histological changes in the ventricular myocardium of VSD patients. It will need to be carefully investigated whether the elevation of cTnI in children with VSD affects their prognosis. The results presented by Sugimoto et al provide some interesting questions to clear up: (1) How do the cTnI levels in patients with VSD change after pulmonary artery banding or intra-cardiac repair? (2) What are the cTnI levels in children with other congenital heart diseases? (3) Does the presence of cTnI in children with congenital heart disease predict their short- and long-term outcomes? (4) Can we use the cTnI level as a biomarker for pediatric heart failure, similar to B-type natriuretic peptide or NT-proBNP?

Finally, it should be noted that highly sensitive cTnI is not only a necrotic marker, but a dynamic marker of myocardial damage. Thus, the clinical relevance of increased cTnI levels in patients with congenital heart disease before and after surgery should also be studied further.

References