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STATE-OF-THE-ART PAPER

Exercise-Induced Cardiac Troponin Elevation

Evidence, Mechanisms, and Implications

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Regular physical exercise is recommended for the primary prevention of cardiovascular disease. Although the high prevalence of physical inactivity remains a formidable public health issue, participation in exercise programs and recreational sporting events, such as marathons and triathlons, is on the rise. Although regular exercise training reduces cardiovascular disease risk, recent studies have documented elevations in cardiac troponin (cTn) consistent with cardiac damage after bouts of exercise in apparently healthy individuals. At present, the prevalence, mechanism(s), and clinical significance of exercise-induced cTn release remains incompletely understood. This paper will review the biochemistry, prevalence, potential mechanisms, and management of patients with exercise-induced cTn elevations. (J Am Coll Cardiol 2010;56:169–76) © 2010 by the American College of Cardiology Foundation

The role of exercise in the prevention, management, and treatment of cardiovascular disease has been well-described (1). Although regular exercise training reduces cardiovascular disease risk, recent studies have documented elevations in biomarkers consistent with cardiac damage (i.e., cardiac troponin [cTn]) after bouts of prolonged exercise in apparently healthy individuals (2–5).

cTns are highly specific markers of myocardial cell damage (6) and are central to the diagnosis of acute coronary syndromes (ACS) (7). cTn elevation is also apparent in conditions that result in significant cardiac stress in the absence of obstructive coronary disease (8). Even minor elevations in cTn confer worse prognosis in patients across a wide spectrum of disease processes (9–11). Accordingly, increased cTn levels after exercise can generate clinical concern and subject athletes to unnecessary hospital admissions and invasive procedures (12). Although numerous studies have reported the release of cTn after exercise, there is no consensus regarding the prevalence, mechanisms, and clinical management of exercise-induced cTn release. This review will address cTn biochemistry and present potential mechanisms for exercise-induced cTn release. In addition, we will summarize the available data characterizing exercise-induced cTn release and provide suggestions on the management of patients with cTn elevation after exercise.

Troponin Biochemistry and Routine Clinical Use

Structure and function. The myocardial sarcomeric unit consists of 7 actin monomers, double-stranded tropomyosin, and a troponin complex (6). The troponin complex is tadpole-shaped (Fig. 1) and is composed of 3 subunits: troponin T (TnT) (37 kDa), which anchors the complex to the tropomyosin strand of the thin filament; troponin C (TnC) (18 kDa), which binds calcium ions released from the sacroplasmic reticulum; and troponin I (TnI) (22.5 kDa), which inhibits the enzymatic hydrolysis of adenosine triphosphate that powers muscle contraction. The globular head of the troponin complex comprises TnC, TnI, and the C-terminal portion of TnT, whereas the tail comprises the N-terminal portion of TnT. Most (>90%) cTn is bound to tropomyosin on the thin filament of the myofibril, with the remainder accounted for by a small unbound cytosolic pool (13). Currently, the function of this pool is not known but might serve as a reservoir for repair/regeneration of tropomyosin-bound troponin.

Ontogeny and cardiospecificity. Cardiac and skeletal muscle share a common developmental pathway but originate from different embryonic precursors (14). Consequently, different forms of TnT and TnI are found in cardiac and skeletal muscle with cardiac (c) and skeletal (s) isoforms of TnT (cTnT, sTnT) and TnI (cTnI, sTnI) each encoded by separate genes. The cTnT and cTnI follow distinct pathways during fetal development. During fetal

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Abbreviations and Acronyms

ACS = acute coronary syndrome

CK-MB = creatine kinase-myocardial band

cTn = cardiac troponin

cTnI = cardiac troponin I

cTnT = cardiac troponin T

muscle development, 3 distinct TnT protein isoforms (cardiac, fast twitch skeletal, and slow twitch skeletal) are expressed simultaneously. A fourth isoform, fetal cTnT, is transiently expressed (15) but is ultimately absent in adults (16). Studies have reported that the cTnT gene is expressed in low concentrations in cardiac and skeletal muscle until mid-fetal development, at which point the cTnT gene is upregulated in cardiac myocytes and suppressed in skeletal myocytes (17). Conversely, cTnI is not expressed in the myocardium during fetal development and is only detectable in adult cardiac tissue (18). In the absence of cTnI, slow twitch sTnI dominates during fetal cardiac development until ultimately replaced by cTnI during the first 9 months of life (19).

Although skeletal and cTn proteins demonstrate a significant degree of amino acid sequence homology, more than 100 differences exist between the 2 tissue-specific isoforms. With the unique amino acid sequences, monoclonal antibodies have been produced against human cTnT and cTnI, respectively. These antibodies form the basis of the highly cardiac-specific immunoassay methods available to detect cTn. The progressive increase in specificity for both cTnT and cTnI assays has been reviewed previously (6).

Release kinetics and routine clinical use. In ACS, cTn is released from the myocardium into the circulation during the first few hours after the onset of ischemia in a biphasic manner. A small initial release of cTn is followed by a larger sustained release with a peak in serum concentration at 12 to 24 h. The initial rise in serum cTn seems to originate from the cytosolic pool with the later rise attributable to release of bound cTn (20). Although debated, the initial release of cytosolic cTn with ischemia might be due to changes in myocardial membrane permeability, whereas the release of bound cTn requires proteolytic degradation and cellular necrosis (21). The half-life of cTnT in the circulation is 120 min (22); the half-life of cTnI is presently not known.

Troponin testing is an invaluable tool for evaluating patients with ischemic chest pain or other clinical syndromes. The sensitivity and specificity of cTnT and cTnI for the detection of myocardial injury is superior to older biomarkers, including lactate dehyrdogenase, creatine kinase, creatine kinase-myocardial band (CK-MB), and myoglobin. The cTn measurement is a component of the universal definition of acute myocardial infarction (7). The release of cTn due to pathologic myocardial damage can be divided into 3 mechanistic categories (23). Primary ischemic cardiac injury describes cTn release from injury caused by a ruptured coronary arterial plaque and coronary occlusion. Secondary ischemic cardiac injury describes myocardial ischemia with myocyte injury in the absence of atherosclerotic plaque rupture and due to increased myocardial oxygen demand that outstrips myocardial oxygen supply. Nonischemic cardiac injury describes cTn release caused by direct damage to the myocardium, including blunt trauma (24), penetrating trauma (25), myocarditis (26), or drug and toxin-induced cardiotoxicity (27). At the present time, the release of cTn by healthy individuals after exercise cannot be explained by any of these pathophysiologic scenarios.

Biomarkers of Myocardial Injury in Exercise

Historical perspective. Early reports of post-exercise elevations in serum concentrations of the myocardial band isoform of creatine kinase (CK-MB) (28) after the completion of endurance events led to concern that such activities could result in cardiac injury. However, elevations in serum CK-MB after prolonged exercise lack specificity for the detection of cardiomyocyte damage (29). The CK-MB is increased in the skeletal muscle of distance runners (30) perhaps because of increases in satellite cells, which repair injured skeletal muscle (31). Therefore, it is likely that individuals with significant exercise training exposure have relatively high skeletal muscle concentrations of CK-MB, which is released during subsequent exercise-induced muscle damage. Thus, in the investigation of exercise-induced cardiac injury, attention shifted from CK-MB to cTn, a highly specific marker of cardiac muscle damage, even in the presence of significant skeletal muscle breakdown (32).

Early generation cTn assays: skeletal protein cross-reactivity. Immunoassays for the quantification of serum cTn isoforms (both T and I) were developed in the late 1980s and became commercially available in the U.S. and Europe in the mid to late 1990s. The first-generation cTnT immunoassay used bovine cTnT as the reference material and cross-reacted with human sTnT (33). Therefore, these

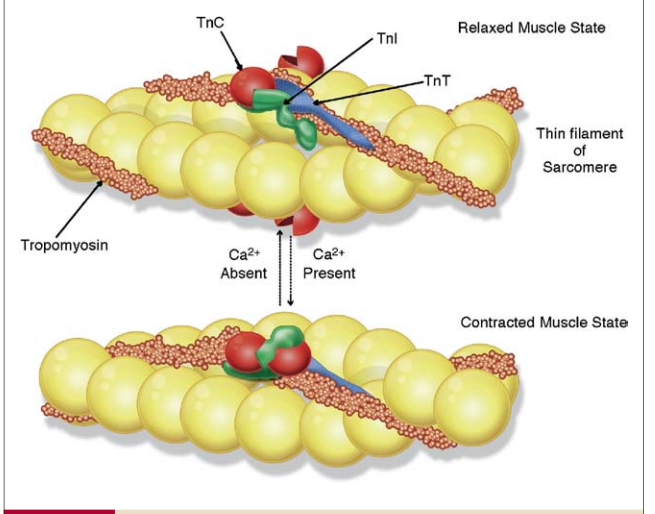

Figure 1 Schematic of Cardiac Muscle

Schematic of cardiac muscle showing location of cardiac troponin I (TnI), cardiac troponin T (TnT), and troponin C (TnC) in relation to actin and tropomyosin. Figure illustration by Craig Skaggs.