Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 24, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.11.066

Biomarkers

Myocardial Ischemia Induced by Rapid Atrial Pacing Causes Troponin T Release Detectable by a Highly Sensitive Assay

Insights From a Coronary Sinus Sampling Study

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Objectives The purpose of this study was to assess whether: 1) very small increases in troponin T, measured by a new highly sensitive cardiac troponin T (hs-cTnT), may reflect ischemia without necrosis; and 2) serial changes can discriminate ischemia from other causes of cardiac troponin T (cTnT) release.

Background A new hs-cTnT assay offers greater sensitivity than current assays.

Methods Nineteen patients referred for diagnostic catheterization underwent cannulation of the coronary sinus (CS). Serial CS and peripheral plasma samples were obtained at multiple time points during and after incremental rapid atrial pacing. cTnT was quantified using both a standard and a pre-commercial highly sensitive assay. Ischemia was determined by the presence of significant coronary artery disease (CAD) and myocardial lactate release with pacing.

Results cTnT concentrations in CS blood increased from a median of 6.8 pg/ml prior to pacing to 15.6 pg/ml 60 min after termination of rapid atrial pacing ($p < 0.0001$), changes that were mirrored at 180 min in peripheral blood (5.1 to 11.8 pg/ml, $p < 0.0001$). Although peripheral cTnT concentrations tended to be higher at 180 min following pacing for patients with CAD and lactate elution ($n = 7$) when compared with those without either marker ($n = 5$) (25.0 pg/ml vs. 10.2 pg/ml, $p = 0.10$), relative (1.7-fold vs. 5.2-fold) and absolute (6.8 pg/ml vs. 8.8 pg/ml, $p = 0.50$) changes were not different between groups.

Conclusions Brief periods of ischemia, without frank infarction, cause low-level cTnT release, and small increases are common after periods of increased myocardial work, even among patients without objective evidence of myocardial ischemia or obstructive CAD. Additional research is needed before hs-cTnT assays are widely adopted in the management of subjects with chest pain syndromes. (J Am Coll Cardiol 2011;57:2398–405) © 2011 by the American College of Cardiology Foundation

Cardiac troponin I and T are currently the preferred biomarkers for the detection of myocardial infarction (1,2), having supplanted older biomarkers, such as creatine kinase (CK) and its MB fraction, due to superior sensitivity and specificity. Furthermore, troponin concentrations provide powerful prognostic information across a spectrum of disease states, even at the lower limit of detection of current assays (3–6).

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Manuscript received September 4, 2010; revised manuscript received October 19, 2010, accepted November 18, 2010.

Given the important information that is provided by the detection of low levels of troponin, interest has focused on using higher sensitivity assays to detect even lower concentrations of this biomarker. Recently, a highly sensitive cardiac troponin T (hs-cTnT) has been shown to have favorable test characteristics compared with traditional less sensitive assays (7,8). Moreover, measurable troponin concentrations with these highly sensitive assays, below the detection range of standard assays, independently associate with an adverse prognosis in patients with acute coronary syndromes (9), chronic coronary artery disease (CAD) (10), and chronic heart failure (11).

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Although troponin elevation above thresholds of detection using current generation assays has become synonymous with "myonecrosis," it is less clear whether low levels of troponin detected with assays that are more sensitive may result from ischemia without necrosis. Moreover, although it has been recommended that dynamic changes in troponin concentrations over short periods of time may be useful for distinguishing ischemia from other causes of troponin elevation (12), few data are available to support this recommendation. To address these questions, we sought: 1) to quantify myocardial release of cardiac troponin T (cTnT) using a new highly sensitive assay during induced ischemia in a controlled human model; and 2) to correlate troponin release with objective indicators of ischemia.

Methods

Patient population. Consecutive patients with stable angina referred for coronary angiography at Parkland Memorial Hospital from November 2002 through April 2004, were approached for enrollment in this study. Those with valvular disease, atrial fibrillation, previous coronary artery bypass graft surgery, a history of heart failure, acute coronary syndrome (ACS), or baseline left bundle branch block were excluded. The protocol was approved by the University of Texas Southwestern Institutional Review Board, and all subjects provided written informed consent.

Abbreviations and Acronyms

CAD = coronary artery disease
CK = creatine kinase
CS = coronary sinus
cTnT = cardiac troponin T
hs-cTnT = highly sensitive cardiac troponin T
LVEF = left ventricular ejection fraction

Study protocol. All patients had beta-blockers and nitrates held for ≥24 h before catheterization. A baseline electrocardiogram was recorded in all patients. A 6-F arterial cannula was placed in the brachial or femoral artery. A 7-F Zucker catheter was advance to the coronary sinus (CS) from a brachial vein, and its position was confirmed by fluoroscopy and oximetry. A baseline set of peripheral arterial and CS blood samples were obtained. Following the acquisition of baseline blood samples, the atrium was paced at 20 beats/min above the resting heart rate, and the pacing rate was increased by 20 beats/min every 3 min until the patient developed: 1) angina-like chest pain; or 2) a target heart rate of 160 beats/min. Atropine (0.5 to 1 mg) was administered as needed if atrioventricular block developed. A 12-lead electrocardiogram and a matched set of arterial and CS blood samples were obtained at this peak heart rate. Additional paired CS and arterial blood samples were obtained at 30 and 60 min following cessation of pacing, after which the CS catheter was removed. Coronary angiography was then performed to define coronary anatomy. Additional samples of peripheral blood were obtained at 180 and 360 min following cessation of pacing. The study schema is depicted in Figure 1.

Biomarker assessment. Blood samples were collected into ethylenediaminetetraacetic acid (EDTA) and serum separator tubes and placed in an iced saline bath until processing occurred, which was within 1 h of collection. Samples were centrifuged, after which the plasma and serum components were removed by pipette, aliquoted into plastic storage tubes, and stored at −70°C until assays were performed. Plasma samples underwent a single thaw cycle for all measurements. Concentrations of troponin T were determined using both a conventional fourth-generation assay (Elecsys cTnT, Roche Diagnostics, Indianapolis, Indiana) and a pre-commercial highly sensitive assay (Elecsys-2010 Troponin T hs STAT, also from Roche Diagnostics). The

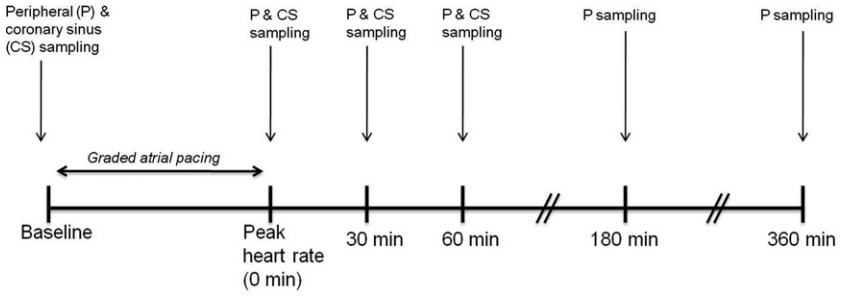

Figure 1 Study Schema