



CARDIOTHORACIC ANESTHESIOLOGY:

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Early Diagnosis of Perioperative Myocardial Infarction After Coronary Bypass Grafting: A Study Using Biomarkers and Cardiac Magnetic Resonance Imaging

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Background. Myocardial injury related to coronary artery bypass grafting (CABG) is poorly characterized, and understanding the characteristic release of biomarkers associated with revascularization injury might provide novel therapeutic opportunities. This study characterized early changes in biomarkers after revascularization injury during on-pump CABG.

Methods. This prospective study comprised 28 patients undergoing on-pump CABG and late gadolinium enhancement (LGE) cardiac magnetic resonance imaging (CMRI) who underwent measurements of cardiac troponin I (cTnI), creatine kinase-MB, and inflammatory markers (C-reactive protein, serum amyloid A, myeloperoxidase, interleukin 6, tumor necrosis factor- α , matrix metalloproteinase 9a, monocyte chemoattractant protein-1, plasminogen activator inhibitor-1a) at baseline, at 1, 6, 12, and 24 hours, and at 1 week (inflammatory markers only) post-CABG. Biomarker results at 1 hour were studied for a relationship to new myocardial infarction as defined by CMRI-LGE, and the diagnostic utility of combining positive biomarkers was assessed.

Results. All patients had an uneventful recovery, but 9 showed a new myocardial infarction demonstrated by new areas of hyperenhancement on CMR. Peak cTnI at 24 hours ($p = 0.66$, $p < 0.001$) and CK-MB ($p = 0.66$, $p < 0.001$) correlated with the amount of new LGE. At 1 hour, 3 biomarkers—cTnI, interleukin 6, and tumor necrosis factor- α —were significantly elevated in patients with vs those without new LGE. Receiver operating curve analysis showed cTnI was the most accurate at detecting new LGE at 1 hour: a cutoff of cTnI exceeding 5 $\mu\text{g/L}$ at 1 hour had 67% sensitivity and 79% specificity for detecting new LGE.

Conclusions. Unexpected CABG-related myocardial injury occurs in a significant proportion of patients. A cTnI test at 1 hour after CABG could potentially differentiate patients with significant revascularization injury.

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Surgical trauma and cardiopulmonary bypass (CPB) contribute to a systemic inflammatory response measurable by circulating cytokines [1–5]. This can be the result of many factors, including contact of blood with the

bypass circuit, myocardial ischemia during bypass, aortic cross clamping, and reperfusion injury [6–9]. Perioperative myocardial infarction (MI) results in further elevation of inflammatory markers [10, 11]. Substantial biomarker elevations have been shown to be prognostically significant [12–15] and usually represent coronary artery bypass grafting (CABG)-related MI [16–18].

Identifying CABG-related MI using conventional electrocardiogram (ECG) and biochemical methods is diffi-

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ARB	= angiotensin II receptor blocker
AUROC	= area under the receiver operating characteristic curve
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
CK-MB	= creatine kinase MB
CMRI	= cardiac magnetic resonance imaging
CRP	= C-reactive protein
cTnI	= cardiac troponin I
ECG	= electrocardiogram
IL-6	= interleukin 6
LGE	= late gadolinium enhancement
LIMA	= left internal mammary graft
LM	= left main
MI	= myocardial infarction
NPV	= negative predictive value
PPV	= positive predictive value
SVG	= saphenous vein graft
SYNTAX	= Synergy between PCI with TAXUS drug-eluting stent and Cardiac Surgery
TNF- α	= tumor necrosis factor- α

cult. Cardiac troponin I (cTnI) is a particularly sensitive biomarker introduced predominantly for risk stratification in patients with acute coronary syndrome and is the gold standard for identifying myocardial necrosis or infarction. However, there is uncertainty about what absolute level of biomarker elevation reflects MI after CABG. Furthermore, there are little data on whether an early measurement of biomarkers (at 1 hour or less after CABG) can provide any diagnostic value.

The joint American College of Cardiology Foundation, American Heart Association, European Society of Cardiology, and World Heart Federation task force recently established definitions for periprocedural necrosis and periprocedural infarction [19]. The universal definition states that cTnI is the preferred biomarker, and that post-CABG biomarker values exceeding the 99th percentile of the normal reference range represent myocardial necrosis. The diagnosis of CABG-related MI (type 5) requires biomarker values more than five times the 99th percentile during the first 72 hours after CABG, together with the appearance of new pathologic Q-waves or new left bundle branch block, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium [19].

Early biochemical identification of MI may enable strategies designed to limit injury, because ECG changes are commonly nonspecific. We hypothesized that certain biomarkers of injury and inflammation might provide a useful diagnostic tool for early detection of periprocedural MI after CABG. Using late gadolinium enhancement (LGE) cardiovascular magnetic resonance imaging (CMRI) and biomarkers of injury and inflammation, we investigated the incidence and early predictors of MI type 5 in patients undergoing CABG.

Material and Methods

The Myocardial Injury following Coronary Artery Surgery versus Angioplasty trial (prospectively registered: <http://www.controlled-trials.com/ISRCTN25699844>) was a prospective, single-center, randomized (1:1) trial of myocardial injury after percutaneous coronary interventions compared with CABG. The primary end point was myocardial injury defined by cTnI level and CMRI. The local ethics committee approved the study, and informed written consent was obtained from each patient.

Treatment and Procedures

A detailed description of the study procedures can be found elsewhere [20]. Briefly, patients undergoing CABG ceased all antiplatelet agents at least 2 days before the operation. General anesthesia was administered. CABG was performed with CPB using nonpulsatile flow and a membrane oxygenator. The core patient temperature was allowed to drift down to a minimum of 32°C. Myocardial protection was achieved with antegrade-delivered cold crystalloid cardioplegia. All patients received at least one pedicled internal thoracic artery graft to the left anterior descending coronary artery and long saphenous vein grafts to branches of the right or circumflex coronary arteries, or both.

CMRI Protocol, Postprocessing, and Data Analysis

Patients were studied at 1.5-T (Sonata, Siemens Healthcare, Erlangen, Germany). The baseline CMRI assessment was performed in the fortnight before revascularization. Repeat CMRI was performed at 7 days (range, 4 to 10 days) and at 6 months after the revascularization. LGE imaging was performed as previously described [21, 22].

Two experienced observers, who were blinded to patient data, interpreted the LGE images. When measurements were different, a third observer performed a review and a consensus was obtained. Areas of LGE were quantified using customized MATLAB R2007b software (MathWorks, Natick, MA) with computer-assisted planimetry of short-axis images. The minimum detectable limit of LGE necrosis using this method of LGE imaging is a group of 10 hyper-enhanced pixels—a voxel of $1.9 \times 1.4 \times 7$ mm.

Measurement of cTnI and Creatine Kinase-MB

Plasma samples for cTnI and creatine kinase (CK)-MB were obtained at baseline and at 1, 6, 12 and 24 hours postprocedure. Automated chemiluminescent immunoassay techniques were used to quantify cTnI and CK-MB on the Siemens ADVIA Centaur (cTnI-“Ultra” for most) and Siemens IMMULITE, respectively (both Siemens Healthcare Diagnostics, Frimley, UK). The ADVIA Centaur cTnI-Ultra assay has a 10% imprecision at 0.05 $\mu\text{g/L}$, with a 99th percentile upper reference limit of 0.06 $\mu\text{g/L}$. The IMMULITE CK-MB assay has a 99th percentile upper reference limit of 4.8 $\mu\text{g/L}$, with less than 10% imprecision at this level.

Initial analyses were performed with the Siemens ADVIA Centaur assay, before the release of the new highly sensitive ADVIA Centaur cTnI-Ultra. To meet guideline requirements of less than 10% imprecision at all reported biomarker levels, repeat analysis of the

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