Heart-Type Fatty Acid Binding Protein and Ischemia-Modified Albumin for Detection of Myocardial Infarction After Coronary Artery Bypass Graft Surgery

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Background. **Heart-type fatty acid binding protein (*h*FABP) and ischemia-modified albumin (IMA) have been put forward as novel biomarkers to detect myocardial injury shortly after onset of ischemia. We compared *h*FABP and IMA with cardiac troponin I (cTnI) for speed and reliability in the diagnosis of perioperative myocardial infarction (PMI) after coronary artery bypass graft surgery (CABG).**

Methods. **In all, 210 consecutive patients undergoing isolated CABG with cardiopulmonary bypass were enrolled in a prospective study. Blood samples were taken perioperatively and throughout the first 72 hours after surgery; clinical data and events were recorded. In cohort A, serum concentrations of *h*FABP and cTnI were measured using a combined quantitative bedside assay. In cohort B, IMA and cTnI serum concentrations were measured using an albumin cobalt binding test. Perioperative myocardial infarction was defined using a cTnI cutoff of greater than 10.5 ng/mL occurring within 24 hours of CABG or new electrocardiographic changes.**

Results. **In cohort A, 14 patients were identified with PMI (group 1), whereas 94 had no PMI and served as controls (group 2). Both *h*FABP and cTnI were increased in group 1 as compared with group 2 ($p < 0.001$). Although cTnI did not differ before 12 hours, *h*FABP diverged much earlier, at 1 hour postoperatively ($p < 0.001$). An *h*FABP concentration of 20 μg/mL at 1 hour detected PMI with an area under the curve of 77.1%. In cohort B, 18 patients were identified with PMI (group 3), and 84 patients served as controls (group 4). No difference in cTnI values could be observed between the groups until 12 hours postoperatively. Ischemia-modified albumin failed to differentiate at any postoperative time point; the low discriminative power of IMA was confirmed with an area under the curve of 53.3% at 1 hour, 48.5% at 6 hours, and 39.3% at 12 hours postoperatively.**

Conclusions. **Heart-type fatty acid binding protein is a sensitive and rapid biomarker that detected PMI reliably at 1 hour after CABG, much earlier than cTnI. The diagnostic value of IMA for detection of PMI appears to be very limited in this setting.**

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Perioperative myocardial infarction (PMI) is one of the most serious complications after coronary artery bypass graft surgery (CABG) and a major cause of short- and long-term morbidity and mortality [1–5]. The early detection of PMI is important for optimal postoperative patient management. Early reintervention such as coronary artery stenting or even immediate reoperation may limit or salvage myocardial damage, improving patient outcome [5–7]. Although established biomarkers, such as cardiac troponin I (cTnI) and cardiac troponin T, have been shown to be highly sensitive and specific to detect PMI after CABG, we recently demonstrated [5, 7] that troponins rise slowly after surgery, delaying diagnosis, and thereby reducing the effectiveness of rescue reintervention strategies. The advent of rapid biomarkers for early onset of myocardial ischemia or infarction such as heart-type fatty acid binding protein (*h*FABP) [8–11] and ischemia-modified albumin (IMA) [12–15], which have recently been reported to detect myocardial ischemia within the first 30 minutes, may enable early reintervention aimed at restoring myocardial perfusion and hence, further optimizing a patient's prognosis [5, 6].

The purpose of the present study was to study the ability of novel early biomarkers of myocardial injury, *h*FABP and IMA, to discriminate between patients with and without PMI after CABG surgery when compared

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Abbreviations and Acronyms

ANOVA = analysis of variance
AUC = area under the curve
CABG = coronary artery bypass graft surgery
cTnI = cardiac troponin I
ECG = electrocardiography
*h*FABP = heart-type fatty acid binding protein
IMA = ischemia-modified albumin
PMI = perioperative myocardial infarction

with contemporary determinants of PMI in this setting (cardiac troponin elevation or electrocardiography [ECG] changes, or both) in a prospective observational pilot study.

Patients and Methods

Patients

Between January 2010 and April 2013, a total of 210 patients were prospectively enrolled in the study. Patients were consequently assigned without randomization into two main study groups, cohort A or cohort B. All patients gave written informed consent, and the study was performed with Institutional Ethics Committee approval. All patients more than 18 years of age with double- or triple-vessel coronary artery disease who were scheduled for elective, isolated, primary CABG surgery with cardiopulmonary bypass were considered eligible. Patients were excluded if any of the following criteria were met: (1) emergency surgery; (2) acute coronary syndrome of any kind within the previous 4 weeks; (3) known preoperative renal insufficiency (serum creatinine greater than 200 μmol/L); (4) preoperative inotropic or mechanical circulatory support of any kind; (5) any condition potentially increasing preoperative troponin I concentration, such as percutaneous coronary intervention within the previous 6 weeks; (6) coronary surgery without the use of cardiopulmonary bypass; (7) reoperative procedures; and (8) concomitant surgery.

Clinical Management

Anesthesia was standardized in all patients. Internal thoracic artery and saphenous vein grafts were used as conduits in all patients. Proximal graft anastomoses were performed with partial occlusion of the ascending aorta. Heparin was administered in order to achieve an activated coagulation time above >400 s. Standard cardiopulmonary bypass technique was used with ascending aortic and two-stage venous cannulation. During cardiopulmonary bypass, moderate hemodilution with a hematocrit level of 20% to 25% and mild systemic hypothermia (greater than 32°C) was maintained. Myocardial protection was achieved using antegrade cold crystalloid (Bretschneider) cardioplegic arrest and additional topical cooling with ice slush, and single aortic cross clamping for all distal anastomosis. Intraoperative graft flow measurement (Cardiomed; MediStim, Oslo, Norway) was routinely performed after weaning from cardiopulmonary bypass, just before sternal closure under stable hemodynamic conditions for each graft.

Postoperative management of patients was standardized. Patients were monitored with regard to their systemic arterial pressures (targeting mean arterial pressure of 65 mm Hg or more) and central venous pressure (target 6 to 12 cm H_2O). A pulmonary artery catheter was placed for more advanced monitoring when needed. A 12-lead electrocardiogram was obtained preoperatively, immediately after arrival in the intensive care unit, and at 12, 24, 36, 48, and 72 hours postoperatively. Oral acetylsalicylic acid, 500 mg, and intravenous heparin, 200 to 400 IE/h were administered within the first 6 hours after surgery in the absence of significant bleeding. Patients with evidence of PMI, based on elevation in cardiac troponin levels and new ECG changes, underwent coronary angiography to evaluate for regional ischemia and were considered for percutaneous coronary intervention or surgical revascularization when appropriate.

Blood Sampling and Biochemical Analysis

Serial venous blood samples drawn from each patient preoperatively and postoperatively at 1, 6, 12, 24, 48, and 72 hours were analyzed for cTnI, *h*FABP, and IMA (Fig 1). Venous blood samples were spun at 3,500 U/min for 7 minutes, and the plasma separated and frozen at −80°C until assay. The cTnI concentration was measured using a specific two-side immunoassay (Dimension Flex; Dade Behring GmbH, Marburg, Germany). The detection range for cTnI was 0.04 to 40 ng/mL, requiring further dilutions if necessary. The assay's reference interval was 0.00 to 0.05 ng/mL. A cTnI above 0.1 ng/mL was considered abnormal. The *h*FABP concentrations were measured using a quantitative one-step bedside immunotest kit (CardioDetect combi; Rennessens, Berlin, Germany; since 2011, Randox Laboratories, Crumlin, UK). Venous blood samples were drawn from each patient (70 μL blood volume needed for each test) in cohort A and applied to the designated well in the CardioDetect combi test card. Results were read on a CardioDetect quant reader (Rennessens; since 2011 Randox Laboratories) in 15 minutes. The cobalt binding capacity of albumin was measured to determine levels of IMA using the albumin cobalt binding assay (ACB-test; Iverness Medical, Köln, Germany) on a Cobas MIRA PLUS instrument (Roche Diagnostics, Mannheim, Germany).

Definition of PMI

A PMI (type 5 myocardial infarction) [16, 17] during index hospitalization was considered to have occurred if one or more of the following diagnostic criteria was met: (1) a maximum cTnI serum concentration greater than 10.5 ng/mL during the first 24 hours after CABG; or (2) significant ST-segment deviations, namely, elevations at the J point in two or more contiguous leads with cutoff points of 0.2 mV or more in leads V1, V2, or V3, and 0.1 mV or more in other leads or significant ST-segment depressions or T-wave abnormalities in two or more contiguous leads [4].