Perioperative acute myocardial infarction (AMI) is a serious complication of cardiac surgery, leading to increased morbidity and mortality (1). Currently, the diagnosis of AMI is based on changes in the electrocardiogram and increased release of biochemical markers. However, changes in the electrocardiogram are not sensitive and specific, whereas creatine kinase MB (CKMB) is not cardiac specific (2). The new markers troponin I and troponin T discriminate between myocardial and skeletal muscle damage (3, 4). Coronary artery bypass grafting (CABG) can be performed with or without (“off-pump”) the use of cardiopulmonary bypass (CPB), whereas valve surgery necessitates CPB. During cardiac operations with CPB, the heart is arrested and protected by cardioplegia. During this period the heart is ischemic. At the end of CPB, the heart is reperfused, and cardiac action resumes. This reperfusion after the ischemic period produces myocardial damage and eventually necrosis (5). In contrast, during off-pump CABG, the heart keeps beating, and thus reperfusion injury is avoided (6). Different types of cardiac surgery may therefore produce different release patterns of myocardial damage markers. Moreover, release of these markers in the perioperative period may be caused not only by the surgery itself, but also by myocardial infarction. The cutoff values of the cardiac markers for patients presenting with acute chest pain have already been reported (7–9). In contrast, these values are not well established for patients during and after cardiac surgery. We investigated the release patterns of the biochemical markers total CK, CKMB activity, CKMB mass, troponin I, and troponin T in patients undergoing different types of cardiac surgery without perioperative complications.

After the protocol was approved by the local ethics committee and informed consent was obtained, patients scheduled for CABG with (group A: 25 males; age, 66 ± 9.8 years; 11 females; age, 68 ± 11.2 years) or without (group B: 19 males; age, 61 ± 14.4 years; 4 females; age, 63 ± 5.7 years) CPB, aortic valve replacement (group C: 8 males; age, 67 ± 9.2 years; 6 females; age, 65 ± 15 years), or mitral valve replacement (group D: 6 males; age, 64 ± 13.9 years; 3 females; age, 72 ± 7.6 years) were recruited. All patients had normal renal, hepatic, and cerebral function. Exclusion criteria were recent AMI, unstable angina, and emergency procedures. Anesthesiological (10) and surgical procedures (11, 12) were performed according to a fixed protocol as described earlier. A standardized CPB technique was used in groups A, C, and D (10). Postoperatively, the diagnosis AMI was accepted based on WHO criteria: electrocardiographic changes (new Q-wave >0.4 s, new ST elevation in two or more leads >0.1 mV), and a typical rise and fall of CKMB.

Blood samples were obtained before anesthesia (baseline), at the start of surgery, after release of aortic cross-clamping (CPB) or completion of grafting (off-pump), on admission to the intensive care unit, at fixed times (0200, 0700, 1400, 2100), and on day 2. After centrifugation at 1000g, serum was separated and stored at −20 °C until further analysis. Total CK and CKMB were measured immediately. Total CK and CKMB activity were measured with a Vitros analyzer (Ortho). The cutoff values (COVs) were 70 U/L (men) and 50 U/L (women) for total CK, and 10 U/L for CKMB activity. Troponin I was measured using an Access (7) analyzer (COV, 0.1 μg/L; Beckman) and an AxSYM (8) analyzer (COV, 2.0 μg/L; Abbott Diagnostics Division). CKMB mass (COV, 5.0 μg/L) and troponin T (COV, 0.1 μg/L) were measured on an Elecsys 2010 (9) analyzer (Roche).

Patients were excluded from analysis if they had repeat operations, AMI, or episodes of arrhythmia. Release patterns of the examined markers were smoothed and expressed as the 2.5th, 50th, and 97.5th percentiles of the concentrations according to National Academy of Clinical Biochemistry recommendations (13). The area under the curve (AUC) for each patient was calculated using the trapezium method (14), normalized by dividing the test result by the upper limit of the reference interval (2), and compared using the Mann–Whitney U-test and the Kruskal–Wallis test. Relationships between cross-clamp time and the AUCs were tested using the Spearman rank correlation test. Analysis of covariance (ANCOVA) was used to detect differences between both CPB treatment procedures (CABG and valve replacement), using the cross-clamp time as covariate. If the necessary requirements of ANCOVA (e.g., parallelism) were not fulfilled, the difference between cross-clamp times shorter than or longer than 1 h was examined with the Mann–Whitney U-test. Statistical significance was accepted at P < 0.05.

Six patients in group A and two in group B were excluded. Most markers reached the highest values at 6–8 h after baseline (Fig. 1). The values for patient groups A, B, C, and D were 23, 3.5, 44, and 50 μg/L, respectively, for troponin I (AxSYM); 0.8, 0.15, 2.2, and 2.2 μg/L, respectively, for troponin I (Access); 0.6, 0.15, 1.0, and 1.8 μg/L, respectively, for troponin T; and 34, 8, 80 and 80 μg/L, respectively, for CKMB mass. All measured values, except total CK, were significantly lower in the off-pump group (Table 1). In addition, CKMB activity, CKMB mass, and troponin were significantly lower in the CABG subgroup with one or two anastomoses than in the subgroup with three or more anastomoses (Table 1). All markers except total CK were lower in the CABG groups than in the valve-replacement groups. Comparison between the aortic and mitral valve groups showed no differences in the examined markers. However, taking into account the...
small numbers, a trend toward difference seemed present, which was probably related to the more extensive surgical intervention in the mitral group.

The mean (± SD) cross-clamp times were lower in the CABG group (55 ± 21 min) than in the valve replacement group (81 ± 27 min). The Spearman rank correlation test demonstrated significant relationships (P < 0.001) with the cross-clamp time for all biochemical markers. The markers CKMB mass, troponin I (AxSYM), and troponin I (Access) did not show homogeneity of slopes (parallelism). Comparison between the CABG and valve replacement groups with cross-clamp times shorter than as well as longer than 1 h showed statistical differences only for times longer than 1 h (P < 0.002). In contrast, when we used ANCOVA, troponin T was different for cross-clamp times both shorter than and longer than 1 h.

This study demonstrates that the release patterns of cardiac markers in patients after cardiac surgery depends on the type of surgery. Cardiac troponins I and T were not significantly increased from baseline in the off-pump CABG group. In contrast, all procedures using CPB produced significantly higher values of the examined cardiac markers. Release of troponins in CABG patients was lower than in valve surgery patients. Thus, the lowest values were obtained for the off-pump group, the highest values for patients undergoing valve surgery. The values for the CABG + CPB group were in between.

All patients undergoing heart surgery may experience a certain amount of myocardial injury. This injury is multifactorial. Its causes include use of CPB, surgical technique, manipulation of the heart, aortic cross-clamping, and preexisting coronary artery disease. The amount of

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**Fig. 1.** Smoothed 2.5th, 50th, and 97.5th percentile values of the release patterns of various cardiac markers after four forms of heart surgery. CABG with CPB (group A) indicates CABG with the use of CPB; CABG without CPB (group B) indicates CABG without the use of CPB. AVR, aortic valve replacement (group C). MVR, mitral valve replacement (group D). Units for troponin I (Access and AxSYM), troponin T, and CKMB mass, µg/L; units for time, hours.
cardiac damage is indicated in the AUC of the release pattern of a cardiac marker (15). This study shows that all types of surgery except off-pump CAGB produce increases beyond the upper limit of the reference interval of each cardiac marker and thus produce measurable cardiac damage as a result of the procedure itself. These data show that total CK does not discriminate between the various groups. In contrast to both troponin I methodologies, troponin T discriminates between the CABG patients with one or two, and the CABG patients with three or more distal grafts.

The observed differences in marker release patterns for surgery (e.g., CAGB and valve replacement) with cross-clamp times shorter and longer than 1 h suggest that myocardial damage after cross-clamp times >1 h is not related just to cross-clamping: other factors, such as insufficient cardioplegic protection and severity of left ventricle hypertrophy, may also be involved. Troponin T release was different for all cross-clamp times in CABG surgery. Off-pump CAGB did not produce a significant increase in any of the tested markers. In contrast, patients undergoing CAGB with CPB showed significant increases in the tested markers, whereas valve replacement surgery produced the highest concentrations of cardiac markers. Because of a lack of analytical standardization and calibration of the various cardiac marker methodologies, we recommend that each institution should determine its own release patterns of cardiac markers for cardiac surgical procedures.

References


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<tr>
<th>Markers</th>
<th>1–2 anas b</th>
<th>≥3 anas b</th>
<th>All patients</th>
<th>CABG – CPB c</th>
<th>Aorta VR d</th>
<th>Mitral VR e</th>
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<tbody>
<tr>
<td>Total CK</td>
<td>(n = 10)</td>
<td>(n = 26)</td>
<td>(n = 36)</td>
<td>(n = 23)</td>
<td>(n = 14)</td>
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<td>CKMB activity</td>
<td>61 (29–153)</td>
<td>97 (30–1126)</td>
<td>90 (29–1126)</td>
<td>96 (21–267)</td>
<td>100 (17–354)</td>
<td>132 (26–257)</td>
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<tr>
<td>CKMB mass</td>
<td>12 (7–19')); 16 (7–68);</td>
<td>8 (3–14); 25 (11–138)</td>
<td>45 (16–126)</td>
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<tr>
<td>Troponin T</td>
<td>84 (18–166); 124 (54–241)</td>
<td>106 (18–241)</td>
<td>198 (49–561)</td>
<td>285 (193–662)</td>
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<tr>
<td>Troponin I (AxSYM)</td>
<td>111 (78–242)</td>
<td>151 (67–242)</td>
<td>246 (34–1022)</td>
<td>428 (322–732)</td>
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<tr>
<td>Troponin I (Access)</td>
<td>116 (55–269)</td>
<td>122 (19–532)</td>
<td>288 (85–1621)</td>
<td>252 (146–736)</td>
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</table>

a CABG with CPB.

b Number of anastomoses.
c CABG without CPB.
d Aorta valve replacement.
e Mitral valve replacement.
f Significantly different from CABG + CPB with three or more anastomoses.
g Significantly different from aorta valve replacement and mitral valve replacement.

Table 1. Median AUC (range) of the normalized release patterns from the examined biochemical markers after various forms of cardiac surgery.

International Survey on the Use of Cardiac Markers, Fred S. Apple, Maryann Murakami, Mauro Panteghini, Robert H. Christenson, Francesco Dati, Johannes Mair, and Alan H.B. Wu, on behalf of the IFCC Committee on Standardization of Markers of Cardiac Damage (1 Department of Laboratory Medicine and Pathology, Clinical Laboratories, Hennepin County Medical Center, Minneapolis, MN 55415; 2 Laboratorio Analisi Chimico Cliniche 1, Azienda Ospedaliera ‘Spedali Civili’, 25125 Brescia, Italy; 3 Clinical Pathology, University of Maryland Medical Center, Baltimore, MD 21201; 4 TUV Rheinland Product Safety GmbH, Am Grauen Stein, Cologne, Germany; 5 Institut fur Medizinische Chemie und Biochemie, University of Innsbruck, A-6020 Innsbruck, Austria; 6 Clinical Chemistry Laboratory, Hartford Hospital, Hartford, CT 06102; 7 author for correspondence: fax 39-030-3995369; e-mail panteghi@bshosp.osp.unibs.it)

Monitoring cardiac troponin I (cTnI) or T (cTnT) for the detection of myocardial injury in acute coronary syndromes has been endorsed by the laboratory medicine community (IFCC, AACC, National Academy of Clinical Biochemistry) (1, 2) and the cardiology community (European Society of Cardiology and American College of Cardiology) (3–5). However, little to no information is available regarding the use of troponins or changing trends from traditional enzymatic markers to the use of protein markers, such as cardiac troponins, in clinical and laboratory practice. The primary objective of this study was to survey hospital laboratories for use of cardiac troponin testing as of January 1, 1995 and January 1, 1999. More than 3000 surveys were distributed internationally at the 1999 IFCC meeting in Florence, Italy, by mail in the US to 274 randomly selected hospitals from the AACC directory, and by telephone survey to 17 hospitals in the Minneapolis-St. Paul, MN metropolitan area. The survey primarily addressed the instrumentation and assays used to measure cardiac markers as of January 1, 1995 and January 1, 1999. Results are presented as trends and descriptive findings, and no statistical analyses were performed.

Fewer than 5% of the surveys distributed internationally were received (n = 105), compared with 25% from the US (n = 67), and 100% from the metropolitan telephone surveys. The majority of responding institutions were general hospital laboratories (40%) or university teaching hospitals (35%), with the remainder either regional or county hospitals. Fig. 1 shows the trends and variety of cardiac markers used in 1995 and 1999 internationally and in the US. Internationally, >50% of laboratories used total creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and CKMB by immunoinhibition, with decreases between 1995 and 1999. Substantial increases in the use of cTnI, cTnT, CKMB mass, and myoglobin assays were observed between 1995 and 1999. Although >50% of laboratories in the US used total CK and CKMB mass assays, there was a decrease between 1995 and 1999. The largest increasing trend was for cTnI assays, with an increase from 7 to 62 laboratories between 1995 and 1999. A moderate increase in the use of myoglobin...