Use of Cardiac Troponin I as a Marker of Perioperative Myocardial Ischemia

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Troponin I is a contractile protein comprising three isoforms, two related to the skeletal muscle and one to the cardiac fibers. Cardiac troponin I (CTn I) is specific, without any cross-reactivity with the other two. Several studies have demonstrated its release after acute myocardial infarction. In contrast, CTn I never has been found in a healthy population, marathon runners, people with skeletal disease, or patients undergoing non-cardiac operations. Thus, CTn I is a more specific marker of cardiac damage than common serum enzymes. It is also more sensitive, allowing diagnosis of perioperative microinfarction and detection of acute myocardial infarction much earlier after the onset of ischemia (4 hours). Using a rapid one-step assay, we measured the release of CTn I in two groups of patients after operation: 20 with calcified aortic stenosis and normal coronary arteries (aortic valve replacement group and control group) and 20 undergoing coronary artery bypass grafting. In the overall population CTn I peaked at hour 6 and practically disappeared after day 5. Mean values were higher in the coronary artery bypass grafting group. In the aortic valve replacement group, a positive correlation was found between aortic cross-clamping time and CTn I, which is a reliable marker of cardiac ischemia during heart operations and can be used to evaluate cardioprotective procedures.

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Troponin I is a contractile protein "part of the thin filament regulatory complex (subunits I, C and T) that confers calcium sensitivity to the adenosine triphosphatase activity of the striated muscle actin-myosin complex" [1]. Three isoforms have been described: troponin I-fast and troponin I-slow were discovered exclusively in fast-twitch and slow-twitch skeletal muscle fibers, respectively. The third one, cardiac troponin I (CTn I), was found exclusively in cardiac muscle and clearly was dissimilar from skeletal isoforms, thus making it a specific marker for myocardial damage [1–3]. This specificity is particularly beneficial for patients undergoing cardiac operations, because the value of measurements of serum creatine kinase (CK) and lactate dehydrogenase levels is limited by enzyme release from noncardiac tissues. In fact, CTn I already has been shown to be a highly specific marker of acute myocardial infarction [1–4] and of reperfusion after thrombolytic therapy [1].

The aim of this study was to compare CTn I release after coronary artery bypass grafting (CABG) and after aortic valve replacement (AVR) for calcified aortic stenosis in a control group of patients with normal coronary arteries.

Patients and Methods

Forty patients were studied in two groups. The AVR group included 20 patients scheduled for AVR and suffering from pure calcified aortic stenosis with normal coronary arteries and normal left ventricular ejection fraction. A St. Jude Medical prosthesis (St. Jude Medical, St. Paul, MN) was implanted in all patients. The CABG group included 20 patients scheduled for CABG with two- or three-vessel disease and a preoperative ejection fraction greater than 0.50. Standard cardiopulmonary bypass technique was used in all patients with moderate hypothermia (29° to 30°C). Myocardial protection was achieved by cold crystalloid hyperkalemic solution (modified St. Thomas' solution) and by additional topical cooling: cardioplegic solution was perfused until cardiac arrest and reinjected every 20 minutes during aortic cross-clamping. It was done directly through the coronary ostia when the aorta already had been opened for AVR. In the CABG group an average of 2.6 grafts per patient were performed, and the left internal mammary artery was used in all patients.

Measurements of Cardiac Marker Proteins

Serial venous blood samples were drawn just before cardiopulmonary bypass and after aortic unclamping at 6, 12, and 24 hours, and daily thereafter for 5 days. Cardiac troponin I concentrations were measured by a rapid, sensitive, and highly specific immunoenzymometric assay developed by ERIA Diagnostics Pasteur (Marnela-Coquette, France) [1]. Each standard troponin I or test

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Table 1. Data Comparison Between the Two Groups

Variable	AVR Group	CABG Group	*p* Value
Preoperative data			
Age (y)[a]	63 ± 13	68 ± 7	NS
Sex (ratio)	11/9	16/4	NS
Body area (m^2)[a]	1.7 ± 0.2	1.8 ± 0.1	NS
Sinus rhythm	19	19	NS
Operative data			
ACC time (min)[a]	40 ± 6	33 ± 8	<0.01
CPB time (min)[a]	61 ± 8	67 ± 13	NS
Cardioplegia volume (mL)[a]	910 ± 220	910 ± 45	NS
Presence of EA	11	4	<0.01
No. of electroshocks[a]	1.1 ± 0.7	1.4 ± 0.8	NS
Postoperative data			
Sinus rhythm	19	18	NS
AMI	0	1	...
Acquired BBB	1	1	...
No. of patients requiring drugs	9	5	NS

[a] Results are given as mean ± standard deviation.

ACC = aortic cross-clamping; AMI = acute myocardial infarction; AVR = aortic valve replacement; BBB = bundle-branch block; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; EA = electrical activity during aortic cross-clamping; NS = not significant.

sample was incubated with MAb 8E1 for 15 minutes. After washing, enzyme activity was measured after the addition of substrate (tetramethylbenzydine). The reaction was stopped by adding H_2SO_4, and the absorbance was read at 450 nm on the status spectrophotometer. Creatine kinase isoenzyme MB (CK-MB) level was measured at hour 6 and once a day for 3 days after operation.

Electrocardiogram

A 12-lead electrocardiogram was recorded preoperatively, at 2 hours postoperatively, and then daily postoperatively. Diagnostic criteria for perioperative acute myocardial infarction (AMI) were new Q waves of 0.04 ms or more or a reduction in R waves of more than 25% in at least two leads. Acquired conduction defects, even nonspecific for AMI diagnosis, were considered.

Statistical Analysis

The statistical analysis was performed with BMDP statistical software (BMDP Corp, Los Angeles, CA). The quantitative data of the two groups were compared with a Wilcoxon nonparametric test, because most biochemical values, such as those for CTn I or CK-MB, are not distributed normally. The qualitative data were compared using the χ^2 test. Linear correlation was achieved between the following distributions: between the CTn I serum level of each sample and aortic cross-clamping time, and between the CTn I serum level of each sample and cardiopulmonary bypass time.

Results

Preoperative, operative, and postoperative data are shown in Table 1. In the overall population, mean patient age was 65 ± 11 years. Preoperatively none of the patients had AMI, low cardiac output, or arrythmias, except 1 case of atrial fibrillation in each group. The preoperative status was nearly identical in the two groups according to age, sex ratio, and body area.

In the operative data there was no significant difference between the two groups in cardiopulmonary bypass time, cardioplegia volume, or the number of electroshocks necessary to defibrillate the heart. There were more patients having electrical activity during aortic cross-clamping and before crystalloid reinjection in the AVR group ($p < 0.01$). Aortic cross-clamping time was significantly higher in the AVR group: 40 versus 33 minutes ($p < 0.01$).

There were no postoperative deaths, and the postoperative course was uneventful in nearly all patients. In the CABG group, one micro-AMI, and, in the AVR group, 2 cases of low cardiac output were observed.

There was no significant difference in CK-MB serum concentration between the two groups. At hour 6, where the difference between the two groups was greater, CK-MB concentration was 25 ± 13 IU/L in the AVR group, and 32 ± 16 IU/L in the CABG group ($p > 0.15$).

The mean CTn I concentration values are shown in Figure 1. Serum concentrations of CTn I were less than 0.1 μg/L before cardiopulmonary bypass in all patients. They peaked at the 6th hour after aortic unclamping and progressively decreased to disappear after day 5. They were globally higher in the CABG group than in the AVR group (see Fig 1), despite a shorter cross-clamping time. The CTn I concentration was significantly higher at hour 6 and at hour 12 in the CABG group (1.84 ± 1.10 and 1.58 ± 0.91 μg/L, respectively) than in the AVR group (1.09 ± 0.60 [$p = 0.02$] and 0.95 ± 0.97 μg/L [$p < 0.01$], respectively). The CTn I concentration decreased regularly in later samples, to disappear at day 2.

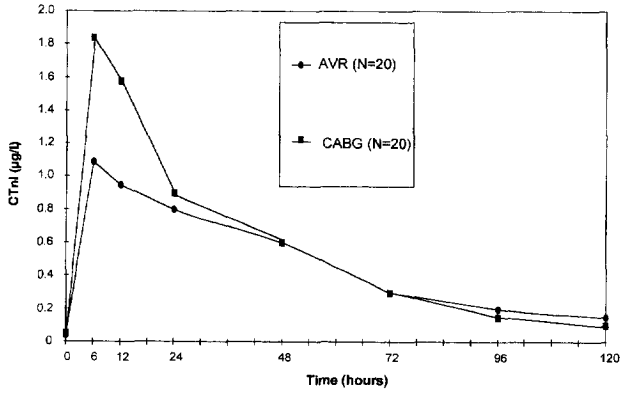

Fig 1. Cardiac troponin I (CTnI) *concentration time courses in aortic valve replacement group* (AVR) *and coronary artery bypass grafting group* (CABG). *Concentrations of CTnI are significantly higher in the CABG group than in the AVR group at hour 6* ($p = 0.02$) *and at hour 12* ($p < 0.01$).

In the AVR group, there was a positive significant correlation ($p < 0.01$) between aortic cross-clamping time and CTn I concentration at hour 6. The regression line equation was CTn I = 0.06 × ACT − 1.4, where ACT was aortic cross-clamping time (minutes). The correlation coefficient was $r = 0.6$, with p less than 0.01. In the CABG group, there was no significant correlation between aortic cross-clamping time and CTn I (data not shown).

Comment

Cardiac troponin I already has been shown to be a specific marker of cardiac damage: there is no cross-reactivity with the skeletal muscle isoforms and it was demonstrated that it does not increase in a healthy population, in marathon runners, or as the result of muscular disease or noncardiac operation [1–4]. The immunoenzymometric assay developed by ERIA Diagnostics Pasteur allows the detection of CTn I within the range of 0.1 to 20 μg/L in 15 minutes at room temperature, making it a fast, sensitive, and specific test.

In our series, the positive correlation between aortic cross-clamping time and CTn I level at hour 6 in the AVR group shows this protein to be a marker of ischemia. In fact, in these patients with normal coronary arteries, the only cause of ischemia was the aortic cross-clamping time. This correlation already has been demonstrated by Katus and associates [5] for troponin T, but less clearly because their population included both normal and narrowed coronary arteries.

In our study, there was no such relation in patients undergoing CABG, which would tend to demonstrate that ischemia in these cases is multifactorial. In addition to cross-clamping ischemia, three other factors are to be considered. (1) Coronary artery stenoses decrease the efficiency of antegrade crystalloid cardioplegia. This factor could have been eliminated by performing retrograde cardioplegia. (2) Although revascularization was as complete as possible, ischemic areas always remain. (3) After the coronary artery bypass grafts have been unclamped, the consequences of reperfusion are not well known. These three factors can explain the early higher concentration of troponin I and are probably responsible for masking the correlation between troponin and aortic cross-clamping time in patients undergoing CABG.

In the case of perioperative myocardial infarction, the peak at hour 6 is higher than in patients without myocardial infarction, and CTn I serum level remains high in all samples until day 5 [6]. The CTn I serum levels are lower in perioperative non–Q-wave myocardial infarction than in perioperative Q-wave MI [6].

In our study 1 patient in the CABG group peaked twice, the second time at day 4 (a value ten times higher than the mean value of the group). He received emergency operation for unstable angina, with a short aortic cross-clamping time (17 minutes), despite which the postoperative electrocardiogram showed the same left bundle-branch block as the preoperative one; such a curve suggests a probable perioperative micro-AMI, undetected by CK-MB, the values of which were normal.

In contrast, a positive correlation in patients with normal coronary arteries shows CTn I to be a marker of ischemia during cardiac arrest and a reliable tool for evaluating and comparing different cardioprotective procedures. Although the early concentration of CTn I appears to be correlated to ischemia, our study could not determine the critical level that could influence the postoperative course.

In conclusion, CTn I already has been shown to be a reliable tool in diagnosing early AMI or perioperative micro-AMI undetectable by electrocardiogram or common serum enzymes. A favorable outcome in most of our patients prevented us from being able to determine the critical level that can influence the postoperative course. Two important facts nevertheless were established in our study: in patients with normal coronary arteries, the release of troponin I was correlated modestly with cross-clamping time, and the concentration of CTn I was higher in the CABG group. These two points suggest that this protein is a marker of cardiac ischemia during operation and as such can be used to evaluate and compare different cardioprotective procedures in routine cardiac operations and in heart transplantations.

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