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Preoperative Myocardial Cell Damage in Patients with Unstable Angina Undergoing Coronary Artery Bypass Graft Surgery

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Background: **Troponin-T is one of the contractile proteins of the myocardium. Its release into the circulation indicates various degrees of myocardial cell damage. Troponin-T may be measured in serum with a recently developed enzyme immunoassay. This immunoassay was used to evaluate the preoperative myocardial cell damage in patients with stable and unstable angina undergoing elective coronary artery bypass graft surgery, and it was compared with conventional assays of creatine kinase (CK) MB isoenzyme activity and mass.**

Methods: **Twenty-one patients with unstable angina and 31 with stable angina were studied. Troponin-T, CK-MB activity, and CK-MB mass were measured 24 h before anesthesia and surgery, immediately before induction of anesthesia, before and after cardiopulmonary bypass, at the end of surgery, and 24 h afterward.**

Results: **In 90% (19 of 21) of the patients with unstable angina, troponin-T was increased 24 h before anesthesia (median 0.33 μg/l, range 0.15–5.2 μg/l), whereas only 3% (1 of 31) of the patients with stable angina had increased values (median 0.0 μg/l, range 0.0–0.53 μg/l). The difference was statistically significant ($P < 0.001$). The same profile was found in patients with and without unstable angina immediately before induction of anesthesia (86% [18 of 21] and 0%, respectively) and before cardiopulmonary bypass (62% [13 of 21] and 0%, respectively). In contrast to troponin-T, CK-MB activity was increased in only 0–14% of patients with unstable angina, and CK-MB mass was increased in only 9–24%. After bypass troponin-T increased in both groups ($P < 0.01$), but there was no longer a statistically significant difference between the groups. Twelver percent (4 of 31) of the patients in the stable angina group and 28% (6 of 21) in the unstable group had major cardiac events (P not significant).**

Conclusions: **The study data suggest that many patients with unstable angina undergoing elective coronary artery bypass graft surgery have already increased troponin-T levels preoperatively, although conventional biochemical markers such as CK-MB activity and mass are at a normal range. Increased troponin-T and normal CK-MB concentrations may reflect some degree of ischemic myocardial cell damage. Because of the small number of patients in the study, the influence of preoperative myocardial injury on perioperative outcome could not be clarified. (Key words: Heart, Perioperative myocardial cell damage: troponin-T. Surgery, cardiac: coronary artery byass graft.)**

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RECENT advances in developing new biochemical assays have identified troponin-T as a highly specific and sensitive marker for myocardial cell damage.[1–3] Troponin-T is a cardiac contractile apparatus protein and is released into the circulation if myocardial ischemia results in either reversible or irreversible cell damage.[4] Circulating troponin-T may indicate such damage even if conventional biochemical assays such as creatine kinase (CK) MB isoenzyme activity or mass are in a normal range.[4–6]

In patients undergoing coronary artery bypass graft surgery unstable angina is reported to be associated with a higher morbidity and mortality compared with stable angina.[7] The extent and the contribution of the preoperative ischemic status and its associated myocardial cell injury, however, could not be quantified with regard to the increased perioperative risk, unless acute myocardial infarction occurred.

Therefore, the aim of this study was to determine if troponin-T could be used as a marker of preoperative myocardial cell damage in patients with unstable angina

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undergoing coronary artery bypass graft surgery and in whom acute myocardial infarction based on electrocardiographic and common biochemical methods was excluded. For comparison, three assays of CK-MB activity and mass were used.

Materials and Methods

After approval by the Ethics committee of the university and informed consent, 52 consecutive patients scheduled for elective coronary artery bypass surgery were enrolled.

The patients were assigned to two groups according to their clinical presentation of angina pectoris. The group of patients with unstable angina was further divided according to the classification of Braunwald[8]: class I (severe or accelerated angina of new onset), class II (subacute angina at rest, not active within the previous 48 h), or class III (angina at rest during the previous 48 h).

Patients with acute or recent myocardial infarction (within the last 6 weeks) as well as those undergoing percutaneous transluminal coronary angioplasty and patients with angina unresponsive to medical therapy and therefore scheduled for urgent operation were excluded. The two criteria for the diagnosis of myocardial infarction were (1) CK-MB activity (Merck) > 12 U/l followed by typical time-dependent changes of cardiac enzymes and (2) development of new Q waves or ST-segment changes persisting for at least 24 h.

Medical treatment of unstable angina included heparin or aspirin. Aspirin was stopped at least 5 days before surgery. Low dose-heparin (10,000 IU per 70 kg per 24 h) was given continuously to the patients designated Braunwald class II and III. <gb>-Blocking agents, calcium-channel antagonists and nitrates, orally or intravenously, were given until the day of surgery.

After oral premedication with 2 mg flunitrazepam all patients received etomidate 300 μg/kg, fentanyl 10 μg/kg for induction of anesthesia, and 0.08 mg/kg pancuronium for paralysis intravenously. Clinical monitoring included seven-lead electrocardiography, arterial pressure, central venous pressure, pulmonary artery pressure, pulse oximetry, and capnography.

Anesthesia was supplemented with isoflurane to 0.5% inspired and bolus doses of fentanyl 50–100 μg intravenously as indicated. Cardiopulmonary bypass was performed with a bubble oxygenator using hemodilution and systemic hypothermia of 25°C. St. Thomas Hospital solution was used for cardioplegia. Conventional 12-lead electrocardiography was performed 24 h before surgery and immediately before induction of anesthesia.

From all patients 10 ml blood was drawn for each sample. Times of blood sampling were defined as follows:

I. 24 h before anesthesia and surgery
II. immediately before induction of anesthesia
III. before cardiopulmonary bypass
IV. after cardiopulmonary bypass
V. at the end of surgery
VI. 24 h after surgery

At measuring points I and II, samples were drawn from a peripheral vein, and at measuring points III–VI samples were drawn from the vena cava superior *via* a central venous catheter.

Biochemical Assays

The biochemical assays were performed without knowledge of the patient's history or perioperative course.

Troponin-T Assay. For the quantitative determination of serum troponin-T, the enzyme-linked immunosorbent assay troponin was carried out with the Enzym-Test-System ES 300 analyzer (Boehringer Mannheim, Mannheim, Germany). The method is based on a single-step sandwich principle with streptavidin-coated tubes as the solid phase and two monoclonal antihuman cardiac troponin-T antibodies. A complete description of the new assay has been given in detail by Katus *et al.*[1,2] The assay is highly reproducible, with coefficients of interassay and interday variation of 0.04 and 0.05, respectively.[1] There is 1% cross-reactivity from human striated muscle.[1] Based on previous studies, values greater than or equal to 0.20 μg/l were considered positive for troponin-T.[9]

Creatine Kinase MB Isoenzyme Activity. Photometric determination of the activity of CK-MB (N-acetylcysteine-activated) on an immunologic basis (Granutest 25, E. Merck, Darmstadt, Germany). The reference range was less than 12 U/l at 25°C.[10]

Percentage of Creatine Kinase MB Isoenzyme to Total Creatine Kinase. Total CK activity was measured by means of an N-acetylcysteine-activated optimized ultraviolet test from Biotrol (Paris, France); CK-MB activity was measured on an immunologic basis as described above.

The calculated percentage of CK-MB to total CK was considered positive if the value exceeded 6%.[11]

Total Creatine Kinase and Creatine Kinase MB Isoenzyme activity. Both CK-MB activity and total CK were measured by means of spectrometric determination (N-acetylcysteine-activated) with use of a clinical chemistry slide containing a dry, multilayered analytical element, coated of a polyester film support (Ektachem 700, Eastman Kodak, Rochester, NY).

Values were considered positive if CK-MB exceeded 16 U/l and the percentage of CK-MB to total CK was greater than 4%.‖

Creatine Kinase MB Isoenzyme Mass Concentration. CK-MB mass was measured by microparticle enzyme immunoassay (Abbott, Abbott Park, IL) for use with the Abbott IMX automated analyzer. Normal range was set at less than or equal to 6 μg/l.[12]

Adverse Outcome and Major Cardiac Events before and after Cardiopulmonary Bypass

Six criteria were used for the definition of major cardiac events:

- perioperative myocardial infarction: based on the appearance of Q waves (new or deepened Q one-third the QRS height and >0.04 s) and increasing CK-MB activity (by immunologic assay, >12 U/l)
- inotropic support: Dopamine or Dobutamine > 10 $\mu g\ kg^{-1}\ min^{-1}$ either during the prebypass period or on the day of surgery
- need for intraaortic balloon pump: indication for intraaortic balloon pump was a low cardiac output of $<2\ l\ min^{-1}\ m^{-2}$ despite pharmacologic support
- malignant dysrhythmias: defined as Lown IV a or Lown IV b arrhythmias
- cardiac death on the day of surgery or the first 24 h postoperatively.

Statistical Analysis

The data are presented as median values and ranges of upper and lower quartiles, because a normal distribution of the data could not be assumed. Nonparametric statistical procedures were used for the same reason. The differences between the stable angina and unstable angina group were tested by the Mann-Whitney test for each measuring point. For testing the differences between two measuring points within each group, the Wilcoxon test for paired differences was applied. Demographic data were tested by the chi-squared procedure and the *t* test.

‖ Ektachem Test methodology. Rochester, NY, Eastman Kodak, 1986.

Results

Thirty-one patients with stable angina and 21 patients with unstable angina were investigated. Demographic and clinical data are summarized in table 1. Five patients with unstable angina were assigned to Braunwald class I, 7 to class II, and 9 to class III. More patients with unstable angina had diabetes mellitus ($P < 0.01$) or were receiving heparin therapy ($P < 0.01$).

In the heparin-treated patients a heparin effect could not be documented by prolongation of partial thromboplastin time. Nitroglycerin therapy was comparable if oral and intravenous therapy was not separated.

Troponin-T concentrations over the complete perioperative period are summarized in figure 1. Each bar represents the median of the values.

Table 1. Demographic and Preoperative Clinical Data of 52 CABG Patients with Stable and Unstable Angina Pectoris

	Stable AP (n = 31)	Unstable AP (n = 21)
Age (yr)		
Mean	60.8	60.9
Range	44–73	50–71
Sex (M/F)	23/8	16/5
Medication use		
Oral nitrates	15	10
Intravenous nitrates	0	7*
Beta-blockers	7	9
Calcium-channel blockers	17	9
Aspirin	0	0
Heparin	0	16*
Hypercholesteremia >200 mg/dl	14	11
Diabetes mellitus	0	5*
Hypertension (>150/90)	0	0
Smoking	0	0
Angiographic findings		
Vessels with stenosis >75% (n)		
1	2	0
2	6	6
3	19	11
Left main CAD (stenosis >50%)	4	4
Previous MI	16	12
Ejection fraction (%)		
Mean	57	60
Range	(37–89)	(42–87)

CABG = coronary artery bypass graft; AP = angina pectoris; CAD = coronary artery disease; MI = myocardial infarction.

* $P < 0.01$.

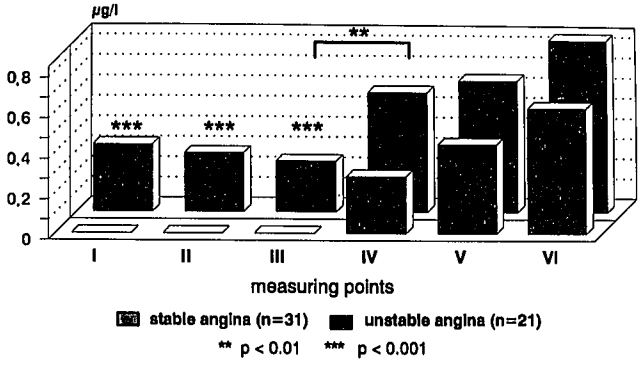

Fig. 1. Troponin-T concentrations (medians) in the two groups at six measuring points. **$P < 0.01$; ***$P < 0.001$.

Ninety percent (19 of 21) of the patients with unstable angina had increased concentrations of troponin-T 24 h before anesthesia and surgery (measuring point I median 0.33 µg/l, range 0.15–5.12 µg/l), whereas 97% (30 of 31) of the patients with stable angina had values less than 0.2 µg/l at the same observation time (median 0.0 µg/l, range 0.0–0.53 µg/l). At the time of induction of anesthesia 85% (18 of 21) patients with unstable angina had increased troponin-T concentrations, (median 0.29 µg/l, range 0.1–1.2 µg/l). All patients with stable angina had normal troponin-T concentrations (median 0.0 µg/l, range 0.0–0.13 µg/l). This statistically significant difference between both groups ($P < 0.001$) did not change before onset of cardiopulmonary bypass. After termination of cardiopulmonary bypass at measuring points IV, V and VI there was a permanent, statistically significant increase of troponin-T in both groups when compared with the prebypass period ($P < 0.01$). At measuring point IV 65% of the patients in the stable angina group had increased troponin-T and 86% in the unstable angina group, at measuring point V 90% and 100% respectively, at measuring point VI 87% and 100 respectively. There was no longer a statistically significant difference between groups.

According to Braunwald classification troponin-T was negative in two of five patients of Braunwald class I at measuring point I, in three at measuring point II, in four at measuring point III, and in two at measuring point IV. Four patients of Braunwald class II were negative at measuring point III and one at measuring point IV. All patients classified Braunwald III were positive throughout the study period.

In contrast to the results for troponin-T, no patient had increased CK-MB activity at measuring point I; one patient had a ratio greater than 6%; and two patients had an increased CK-MB mass. CK-MB values measured with the Kodak assay were 48% less than the Merck assay (overall mean values 6.86 *vs.* 14.2 U/l).

Median values with the upper and lower quartiles of the four assays of troponin-T, CK-MB activity, or CK-MB mass are summarized in table 2.

Table 3 compares the absolute number and the percentage of patients with values above the reference range between troponin-T and the other assays of CK-MB activity and mass. There was no statistically significant difference between CK-MB activity and mass throughout the prebypass period.

For evaluation of the ideal discrimination value of troponin-T between the stable and unstable angina groups, we calculated receiver–operator characteristics for the mean values of the prebypass and postbypass period (fig. 2). A limit value at 0.15 µg/l yields a sensitivity of 95% and a specificity of 97%, whereas 0.2 µg/l results in sensitivity and specificity of 86% and 100% respectively.

Before cardiopulmonary bypass no major cardiac events occurred in either groups. After cardiopulmonary bypass 12% (4 of 31) of the patients in the stable angina group and 28% (6 of 21) of the patients in the unstable angina group had major cardiac events. The difference was not statistically significant. One patient in the stable angina group with malignant dysrhythmias, perioperative myocardial infarction, low cardiac output, and an intraaortic balloon pump died on the day of surgery in the intensive care unit. He had incomplete revascularization, a long bypass time, and difficulty in separating from cardiopulmonary bypass.

Discussion

An ideal marker of myocardial injury should be found in high concentration in myocardium, not be found in other tissues, be released rapidly after myocardial injury, be released in direct proportion to the extent of injury and should persist in plasma for several hours.[13] Troponins meet most of these criteria: based on a myocardial ischemic event the loss of integrity of myocardial cell membranes results in a release of proteins of the cardiac contractile apparatus into the circulation.[1,4] Among these proteins troponin-T and I appear to be unique cardiac antigens. They are not detectable in the serum of healthy people. Specificity is reported to be 100%.[13] After acute myocardial infarction troponins remain present for several days.[6,14] Controversy only

Table 2. Comparison of Median Values and Ranges of Upper and Lower Quartiles of Each Assay in the Stable Angina Group (n = 31) and in the Unstable Angina Group (n = 21) at Measuring Points I–VI

	I	II	III	IV	V	VI
Tropinin T (μg/l)						
Stable						
25%	0	0	0	0.16	0.26	0.29
Median	0	0	0	0.28	0.44	0.62
75%	0.03	0.02	0.03	0.4	0.5	3.37
Unstable						
25%	0.28	0.21	0.15	0.34	0.5	0.6
Median	0.33	0.29	0.25	0.59	0.65	0.85
75%	0.47	0.35	0.32	0.74	0.87	1.17
CK-MB Merck (U/l)						
Stable						
25%	2	3	3	15	18	11
Median	4	5	4	18	20	18
75%	6	6	6	26	31	28
Unstable						
25%	3	3	4	14	18	14
Median	5	4	4	19	22	18
75%	8	7	7	24	26	24
CK-MB Kodak (U/l)						
Stable						
25%	0.4	0.4	0.4	6.1	8.6	3.8
Median	0.5	0.4	0.4	8.6	11.4	8.2
75%	1.9	0.7	0.8	12	19.4	5.3
Unstable						
25%	0.4	0.4	0.4	6	7	2.7
Median	1.1	0.4	0.4	10.2	11.6	4.5
75%	2.2	1.5	1.5	11.3	16.3	6.5
CK-MB mass (μg/l)						
Stable						
25%	0	0	1	10.5	17.5	9.6
Median	0.3	1.1	2.2	14.4	26.1	24
75%	1.6	2.1	3.1	20.9	39.2	64
Unstable						
25%	0	0	1.4	14	21.1	9.2
Median	1.4	0.9	2.9	15.4	30.9	20
75%	2.1	1.9	5.6	24.1	40.8	31

exists in the interpretation of experimental and clinical data that troponin-T could be reexpressed in injured human skeletal muscle whereas troponin-I might be the only molecular marker of myocardial injury that is not expressed in regenerating skeletal muscle.[13,14] Beside high sensitivity and higher specificity[13] the advantage of troponin-T and troponin-I compared with conventional CK and CK-MB assays is the detection and quantification of myocardial cell damage in cases where CK and CK-MB are still in a normal range.[6] Collinson concluded that at present troponin measurement meets the criteria for the best biochemical test for the differential diagnosis of cardiac damage.[15]

This study demonstrates that many patients with unstable angina—although clinically and medically stabilized—undergo anesthesia and surgery already with increased troponin-T concentrations, whereas CK-MB activity or mass is most often normal. The relative ability of a membrane to leak different sized proteins might cause that the small-weighted troponin-T (molecular weight 33,000 Da) is released earlier than the isoenzyme MB (molecular weight 86,000 Da). Myoglobin (molecular weight 17,800 Da) is released even earlier, but with lower specificity.[13]

Unstable angina describes a broad pathophysiologic spectrum ranging from events with increasing fre-

Table 3. Number and Percentage of Patients with Assays Greater than Normal in the Stable Angina Group (n = 31) and in the Unstable Angina Group (n = 21) at Measuring Points I–VI

	I	II	III	IV	V	VI
Troponin (>0.2 μg/l)						
Stable						
n	1	0	0	20	28	27
%	3.2	0	0	64.5	90.3	87.1
Unstable						
n	19	18	13	18	21	21
%	90.5	85.7	61.9	85.7	100	100
CK-MB Merck (>12 U/l)						
Stable						
n	0	0	0	25	29	22
%	0	0	0	80.6	93.5	70.9
Unstable						
n	0	2	3	17	19	16
%	0	9.5	14.3	80.9	90.5	76.2
CK-MB/CK Merck (>6%)						
Stable						
n	0	0	0	10	19	6
%	0	0	0	32.3	61.3	19.3
Unstable						
n	1	3	2	6	15	5
%	4.8	14.3	9.5	28.6	71.4	23.8
CK-MB/CK Kodak (>16 U/l + >4%)						
Stable						
n	0	0	0	5	9	4
%	0	0	0	16.1	29	13
Unstable						
n	0	0	0	3	6	4
%	0	0	0	14.3	28.6	19
CK-MB mass (>6 μg/l)						
Stable						
n	0	1	4	28	29	28
%	0	3.2	12.9	90.3	93.5	90.3
Unstable						
n	2	3	5	18	20	20
%	9.5	14.3	23.8	85.7	95.2	95.2

quency or intensity of ischemia to acute myocardial infarction. Increased CK activity is found in only in a small percentage of patients with unstable angina.[16–19]

Histologic studies revealed myocardial cell necrosis in high-risk patients even if serum CK activity was in a normal range.[19] Technetium 99 pyrophosphate scans also detected subendocardial necrosis in one third of patients with unstable angina.[20]

In the study by Hamm *et al.* 39% of the patients had elevated troponin-T, but only 3% had increased CK-MB activity.[9] It seems likely that the measurement of CK-MB remains a standard biochemical test for the confirmation or exclusion of acute myocardial infarction, however, it fails to prove as an ideal marker for minor myocardial cell damage.[4,14]

Circulating troponin-T may have two origins, one from a smaller free cytosolic pool and one from a larger structurally bound fraction.[21] In patients with acute myocardial infarction a biphasic peak of serum troponin-T was found.[21] The first peak reflects the characteristics of cytosolic proteins like CK beginning about 3.5 h and ending about 32 h after the onset of pain, the second peak indicates a continuous liberation of the bound troponin-T fraction. Because of its short half-life of about 120 min a constant elevation of serum troponin-T indicates a continuous release from the "bound" fraction into the circulation either from an

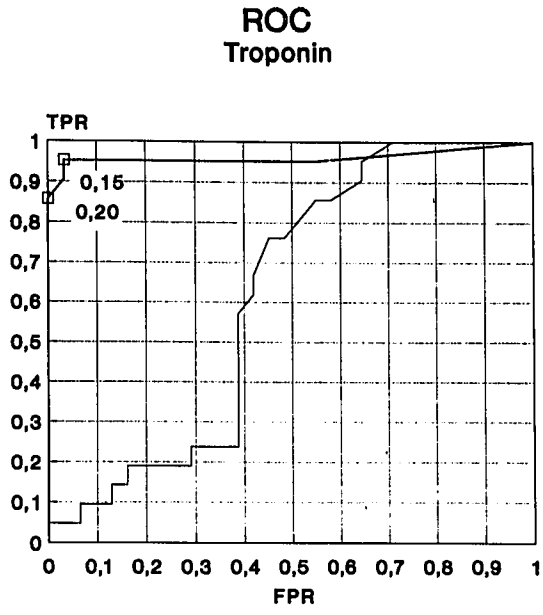

Fig. 2. Receiver–operator characteristics for troponin-T. TPR = true positive rate = sensitivity; FPR = false positive rate = 1 − specificity; bold dashed lines = prebypass means (measuring points I–III); light dashed lines = postbypass means (measuring points IV–VI).

immediately preceding event or from a continued injury.[21]

Currently, it remains unclear whether increased troponin-T concentrations in patients with unstable angina indicate only ischemic cell damage or microinfarctions that are not detectable by conventional diagnostic methods. Hamm *et al.* pointed out that reversible as well as irreversible cell injury may occur in unstable angina.[9] This may be explained by an intermittent critical flow reduction as a result of intracoronary thrombus formation or also by minor local cell necrosis due to thrombotic microembolism. Therefore, we have to assume that most of the patients may have pathophysiologic changes resulting in a continued release of troponin-T into the circulation, although they seemed to be clinically stabilized.

The reason for the higher percentage of patients with increased troponin-T concentrations in our unstable angina group compared with other studies is not clear. Possible mechanisms may be preoperative stress and an inadequate medical pretreatment. Although 76% of our patients with unstable angina were receiving low-dose-heparin this therapy did not result in a prolongation of partial thromboplastin time. Two studies involving more than 800 patients with acute unstable angina have shown that continuous intravenous heparin treatment reduces significantly episodes of ischemia, the frequency of angina, the overall duration of ischemia and the incidence of myocardial infarction if partial thromboplastin time is measurably prolonged to 1.5–2 times baseline.[22,23] Theroux *et al.* demonstrated that in treating unstable angina the disease process may be reactivated within hours of the discontinuation of the drug.[24] It can be speculated that heparin was not administered in a sufficient dose to stop or to control an ongoing ischemic process.

The interpretation of the advantage of CK-MB mass over activity in the diagnosis of acute myocardial infarction is controversial.[14,25] In our study we found a slightly higher sensitivity with CK-MB mass than with CK-MB activity, but it was considerably lower than that of troponin-T. In general, mass and activity assays yield comparable results.[14,25] The pattern of pathologic biochemical findings in the study, indeed confirms the vague, indistinct transition from an undamaged to damaged myocardium in unstable angina.

During cardiopulmonary bypass a further statistically significant increase of troponin-T concentrations could be observed in both groups without a trend to normalization 24 h postoperatively. There are only few data available referring to the bypass period. In a study with 21 patients undergoing coronary artery bypass graft surgery Mair *et al.* have assumed that a significant increase of troponin-T in patients with uncomplicated outcome probably reflects myocardial cell damage from ischemia during cross-clamping.[26] Other mechanisms like reperfusion injury may not be excluded.

In conclusion, the comparison of different markers of ischemic myocardial injury identifies troponin-T as an assay with the highest sensitivity in the preoperative setting of patients with unstable angina undergoing coronary artery bypass graft surgery. The study suggests that many patients, though clinically stabilized, apparently have a minor degree of myocardial cell damage before anesthesia and cardiopulmonary bypass as assessed by elevated troponin-T and normal CK-MB activities.

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