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Cardiac Troponin I and Myocardial Contusion in the Rabbit

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Background: **Patients with cardiac contusion have a high risk of cardiac complications during emergency anesthesia. Despite the progress in cardiac imaging, a biologic marker of myocardial damage such as cardiac troponin I remains useful and has been proposed in clinical practice. The relationship among histologic injury, left-ventricular function, and release of cardiac enzymes and cardiac troponin I has been investigated after a controlled myocardial contusion in a rabbit model.**

Methods: **A global trauma (two levels of energy: 250 and 350 mJ) was produced on an isolated preparation of rabbit's heart, of which the temperature, perfusion flow, beating rate, and left-ventricular volume were kept constant. Left-ventricular pressure and its first derivative as a function of time were measured during a 60-min period after the blow; a timed collection of the effluent was made to assess creatine kinase, lactate dehydrogenase, and cardiac troponin I. At the end of the period, an anatomic score of the contusion was calculated by histologic examination of the hearts.**

Results: **Compared with a control group, the two levels of cardiac trauma resulted in a proportional anatomic injury significantly correlated with left-ventricular dysfunction (Δ%dP/dt$_{max}$ = −16 ± 12 and −36 ± 20% at 3 min, mean ± SD). Transient releases in cardiac markers after the lesser amount of trauma contrasted with a prolonged and biphasic release of cardiac troponin I after the greater amount. Peak cardiac troponin I level was correlated with anatomic injury (ρ = 0.596, P = 0.001) and negatively correlated with left-ventricular dysfunction (r = −0.375, P = 0.04).**

Conclusion: **Cardiac troponin I is a marker of anatomic and functional consequences of experimental cardiac trauma and may be a predictive indicator of early posttraumatic cardiac complications during the postoperative period. (Key words: Contractility, heart trauma, isolated heart, myocardial injury, troponin.)**

THE rate of blunt cardiac injury varies widely among clinical series of trauma patients. It mainly depends on the diagnostic criteria, but 15% seems to be a reasonable estimate.[1] Patients with documented cardiac contusion requiring emergency noncardiac surgery have a high incidence of perioperative hypotension or dysrhythmias.[2–6] Early diagnosis of myocardial contusion is needed in order to identify this subgroup of patients at risk for life-threatening complications.[4,7–9] An accurate biologic indicator of myocardial damage remains a useful tool for the initial screening of patients. The determination of cardiac isoenzymes such as the MB isoform of creatine kinase in patients with frequent concomitant rhabdomyolysis, however, is inadequate.[9,10] New immunoassays allow the detection of circulating structural proteins of the myocardium, which are pertinent markers of myocardial lesion after an ischemic stress. Troponin I is a part of the troponin complex located in the thin filament of striated muscle and regulating the actin-myosin interactions. Cardiac troponin I (cTnI) differs from its skeletal muscle isoforms by a unique amino-terminal sequence never expressed by the developing or pathologic muscle.[11] The measurement of cTnI levels in the serum currently is used as a routine test to detect cardiac injury after trauma.[12,13] To assess the relationship among myocardial injury, cardiac dysfunction, and biologic markers, we measured the effects on total creatine kinase (CK_{tot}) and lactate dehydrogenase (LDH_{tot}) and the concentration of cTnI in the effluent of an isolated preparation of rabbit's heart submitted to a controlled blunt injury. Correlations between these biologic indicators and histologic lesions as well as functional consequences of the injury were investigated.

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Table 1. Hemodynamic Data

	Baseline Values	Time after Cardiac Injury (min) 1	3	5
LVEDP (mmHg)				
Control (n = 9)	3 ± 1	3 ± 1	3 ± 1	3 ± 1
Moderate contusion (n = 9)*	3 ± 2	13 ± 8	11 ± 7	9 ± 6
Severe contusion (n = 14)*†	4 ± 2	17 ± 13	15 ± 12	12 ± 12
LVDP (mmHg)				
Control (n = 9)	95 ± 22	97 ± 21	100 ± 20	100 ± 20
Moderate contusion (n = 9)*	90 ± 15	66 ± 19	68 ± 20	70 ± 25
Severe contusion (n = 14)*	98 ± 19	68 ± 17	61 ± 15	63 ± 22
PP (mmHg)				
Control (n = 9)	54 ± 7	55 ± 8	55 ± 7	56 ± 9
Moderate contusion (n = 9)	41 ± 7	37 ± 14	39 ± 11	38 ± 11
Severe contusion (n = 14)*†	55 ± 8	62 ± 15	61 ± 15	56 ± 13
LVdP/dt max (mmHg/s)				
Control (n = 9)	1,256 ± 210	1,278 ± 199	1,311 ± 209	1,319 ± 196
Moderate contusion (n = 9)*	1,399 ± 236	1,229 ± 289	1,188 ± 322	1,373 ± 508
Severe contusion (n = 14)*†	1,445 ± 218	1,019 ± 294	946 ± 384	1,019 ± 337
LVdP/dt min (mmHg/s)				
Control (n = 9)	1,083 ± 175	1,122 ± 192	1,149 ± 186	1,147 ± 197
Moderate contusion (n = 9)*	991 ± 194	861 ± 311	810 ± 284	941 ± 421
Severe contusion (n = 14)*	1,294 ± 197	875 ± 275	845 ± 350	926 ± 322

* $P < 0.05$ *versus* control group (Newman-Keuls test).

† $P < 0.05$ *versus* moderate contusion group (Newman-Keuls test).

LVEDP = left ventricular diastolic pressure; LVDP = developed pressure; PP = perfusion pressure; LVdP/dt = first derivative of left ventricular pressure as a function of time during contraction (max) or relaxation (min).

Materials and Methods

Langendorff Preparation

All experiments were conducted in a model of isolated rabbit's heart as previously described.[14] Care of the animals was in accordance with the recommendations of the Helsinki Declaration and the guidelines of French regulations for animal experiments. Forty male New Zealand rabbits weighing 1,800–2,500 g were anesthetized with intraperitoneal pentobarbital (60 mg/kg). Tracheostomies were performed and the animals were ventilated with room air (Harvard Rodent Ventilator 683, Ealing, Les Ulis, France). The chest was opened, and the heart was removed after intravenous heparinization (1,000 U) and quickly mounted on the perfusion apparatus. The aorta was cannulated, and the heart was perfused in a retrograde manner at a constant flow of 30 ml/min with a modified Krebs-Henseleit buffer at 37.0 ± 0.1°C without recirculation. The buffer composition was as follows: NaCl: 118 mM; KCl: 4.7 mM; $CaCl_2$: 1.8 mM; $MgSO_4$: 1.2 mM; KH2PO_4: 1.2 mM; $NaHCO_3$: 25 mM; glucose: 5.5 mM; sodium pyruvate: 2.0 mM. Salts in the buffer (Prolabo, Paris, France) were at least of analytic grade and were compatible with cell culture. The buffer was oxygenated (95% O_2–5% CO_2) and the quality of oxygenation was tested regularly with partial pressures of 504 ± 26 mmHg for oxygen and 39 ± 13 mmHg for carbon dioxide and a *p*H of 7.37 ± 0.01. Atrial pacing was done with a bipolar electrode at a cycle interval of 350 ms (170 beats/min) by a Jansen ST 0198 stimulator (Jansen Instruments, Paris, France). A small needle was inserted through the left-ventricular (LV) free wall to detect any significant aortic valve regurgitation.

A compliant balloon catheter (Hugo Sachs Electronik, March-Hugstetten, Germany) was inserted into the left ventricle through the left atrium. After a stabilization period, the balloon was inflated with a constant volume of saline (0.7 ml). The volume of the balloon was not modified until the end of the experiment. LV and coronary perfusion pressures were measured with a Statham P20 transducer (Statham Instruments Inc., Oxnard, CA) and recorded on a Gould 8000s chart recorder (Gould Inc., Cleveland, OH). The first derivative as a function of time of the LV pressure (LVdP/dt) was obtained by electronic differentiation. The pulmonary artery was cannulated for the collection of the effluent perfusate (the coronary effluent flow).

Table 1. Continued

Time after Cardiac Injury (min)				
10	15	30	45	60
4 ± 1	4 ± 2	4 ± 2	5 ± 3	5 ± 3
8 ± 5	7 ± 4	6 ± 3	5 ± 4	4 ± 3
11 ± 12	11 ± 13	9 ± 7	9 ± 8	11 ± 9
101 ± 21	100 ± 15	96 ± 15	97 ± 19	94 ± 17
71 ± 27	77 ± 27	79 ± 26	77 ± 25	80 ± 24
70 ± 17	72 ± 18	73 ± 14	69 ± 13	69 ± 12
59 ± 15	62 ± 17	65 ± 17	68 ± 20	69 ± 22
38 ± 11	38 ± 11	38 ± 11	38 ± 10	40 ± 11
54 ± 12	55 ± 12	56 ± 13	62 ± 21	69 ± 32
1,345 ± 214	1,336 ± 243	1,267 ± 245	1,269 ± 203	1,189 ± 153
1,403 ± 520	1,449 ± 508	1,536 ± 528	1,529 ± 517	1,545 ± 485
1,054 ± 358	1,093 ± 391	1,093 ± 312	1,032 ± 268	1,053 ± 265
1,172 ± 223	1,194 ± 254	1,136 ± 238	1,028 ± 193	947 ± 190
1,011 ± 455	1,084 ± 475	1,088 ± 470	1,067 ± 469	1,112 ± 463
970 ± 339	1,012 ± 337	1,023 ± 291	977 ± 255	907 ± 261

Cardiovascular Parameters and Cardiac Trauma

The following cardiovascular parameters were measured: LV end diastolic pressure; LV developed pressure, calculated as the difference between systolic and diastolic pressures; mean perfusion pressure; and minimum LVdP/dt and maximum LVdP/dt ($LVdP/dt_{max}$). The following criteria for stability of the Langendorff preparation were used: absence of any aortic valve regurgitation, sinus rhythm (before pacing) between 120 and 170 beats/min without arrhythmias, and $LVdP/dt_{max}$ more than 1,000 mmHg/s. After a 15-min stabilization period following instrumentation, basal measurements were made and the contusion was performed. A standardized global injury to the myocardium was produced using an adaptation of the model developed by Baxter *et al.*[15] Briefly, a pendulum weighing 180 g was released from a variable height to give a blow to the isolated heart in the anteroposterior position with the heart maintained against an immobile plate. Two groups were studied initially: 10 hearts served as a control group, and 20 received the blow from a 20-cm height (350 mJ), the severe contusion group. Considering the results, an additional group of 10 hearts received the blow from a 15-cm height [250 mJ], the moderate contusion group. After the blow and a short period of cardiac arrest, the parameters again were measured at frequent intervals over a 60-min period. Because of a sustained tachyarrythmia, a prolonged cardiac arrest (> 15 s), or an aortic tear, eight hearts were discarded (one in the control group, one in the moderate contusion group, and six in the severe contusion group).

Biologic Parameters

Effluent was collected before and at 1, 3, 5, 10, 15, 30, 45, and 60 min after the blow. Samples were stored at −20°C until the assays were performed. CK_{tot} and LDH_{tot} were assessed in duplicate by measurements of catalytic concentrations of enzymes at 37°C according to the recommendations on International Federation of Clinical Chemistry methods. cTnI concentration was measured using fluoroenzymatic method with a commercially available assay (Stratus cTnI, Dade, Maurepas, France). The hearts were weighed after perfusion. CK_{tot} and LDH_{tot} were expressed in units per liter per gram of heart per minute; cTnI was expressed in micrograms per liter per gram of heart per minute. The limit of detection for cTnI was 0.35 μg/l,[16] corresponding to a mean value of $0.04\ \mu g \cdot l^{-1} \cdot g^{-1} \cdot min^{-1}$. cTnI was measured in duplicate, and the mean coefficient of variation was 6.8% in the present study. The areas under the time–activity or time–concentration curves (AUC_{CK}, AUC_{LDH}, AUC_{cTnI}) were computed by the trapezoidal rule. Knowing the constant flow and the absence of recirculation, these AUCs corresponded to the total amount of the biologic cardiac markers released by the hearts during the study period and were

expressed in units per gram for AUC_{CK} and AUC_{LDH} and in micrograms per gram for AUC_{cTnI}.

Histologic Study

At the end of the 60-min experiment, diastolic arrest of the preparations was obtained using the infusion of a calcium-free solution, and the hearts were fixed by a 7.5% formaldehyde solution. Each heart was cut transversally into three slices, which were embedded in paraffin. Sections of 5-μm thickness were obtained from each block and stained with hematoxylin and eosin. In addition, immunohistochemistry was performed as a sensitive marker of early myocyte necrosis. Vinculin antibody (Eurobio, Paris, France) was used to detect the proteins associated with the cytoskeleton. The detection system was biotinylated donkey antimouse immunoglobulin at a dilution of 1:50, followed by fluorescein isothiocyanate–labeled streptavidin at 1:50.[17] On each section, the induced lesions were evaluated semiquantitatively by two independent observers unaware of the study groups using the following scores of severity: 0, no lesion; 1, rare lesions; 2, moderate lesions; 3, extensive lesions. The total range of the histologic score (anatomic injury) was therefore 0 to 9 for each heart.

Statistical Analysis

Data are presented as the mean ± SD. Basal values were compared among the three groups using a Student *t* test for unpaired data with a Bonferroni correction. The normality of hemodynamic and biologic data was checked by visual inspection of the data set and by the Shapiro–Wilk test. A logarithmic transformation then was used as appropriate, and the effects of the blow were compared among groups using an analysis of variance (two ways, one of which repeated) followed by a Newman-Keuls test. Areas under the time–activity or time–concentration curves of biologic parameters were compared among the three groups using a one-way analysis of variance followed by a Newman-Keuls test. Histologic scores were compared among the three groups using a Kruskall–Wallis test followed by a Mann–Whitney *U*-test with a Bonferroni correction. The relationships among cardiovascular parameters, biologic data, and histologic scores were assessed by the rank Spearman correlation test. $P < 0.05$ was considered significant.

Results

The histologic lesions consisted of multiple disseminated foci of myocytes necrosis and cellular fragmentation. Contraction bands were demonstrated within or surrounding the necrosis as a dense transverse cytoplasmic banding extended frequently across the whole myofibers, and they were localized between intercalated discs. Langendorff preparation *per se* resulted in a slight anatomic injury in four out of the nine control hearts.

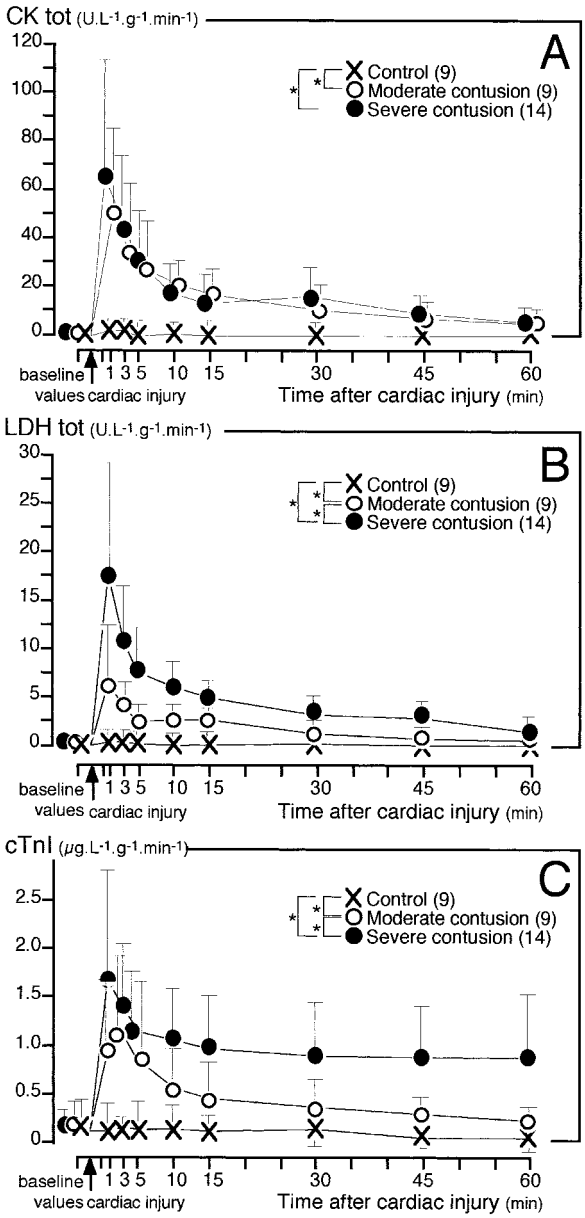

Fig. 1. Evolution of total creatine kinase activity (CK_{tot}; *A*), total lactate dehydrogenase activity (LDH_{tot}; *B*), and cardiac troponin I concentration (cTnI; *C*) in the effluent of the preparations after the blow (cardiac injury) and in the control group. Numbers in brackets give the size of the groups. Newman–Keuls test: *$P < 0.05$ for between-groups comparison.

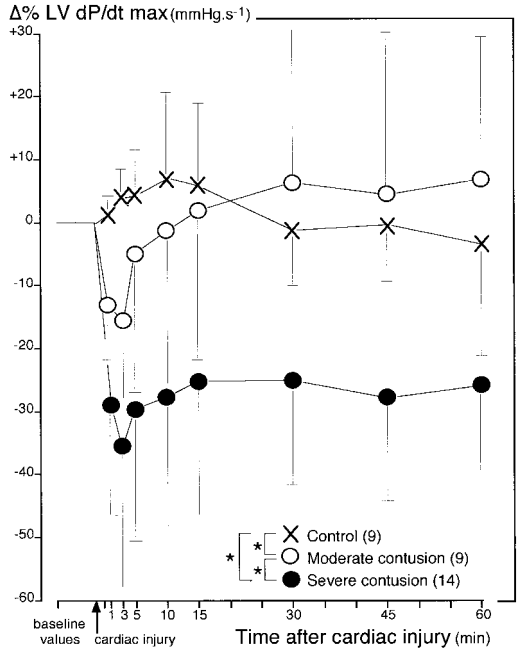

Fig. 2. Relative change (Δ%) in maximum systolic left-ventricular pressure derivative ($LVdP/dt_{max}$) as an indicator of left-ventricular function after the blow (cardiac injury) in the two contusion groups and in the control group. Numbers in brackets give the size of the groups. Newman–Keuls test: *$P < 0.05$ for between-groups comparison.

Nevertheless the median (range) of the histologic score was significantly different between each contusion group and the control one (severe: 6 [0–9], $P = 0.004$; and moderate: 4 [3–5], $P = 0.001$, *vs.* 0 [0–3] for the control group).

There were no significant difference in basal hemodynamics and biologic values among the three groups as demonstrated in table 1 and figure 1. As shown in table 1 and figure 2 the blow was followed by early decreases in $LVdP/dt_{max}$, minimum LVdP/dt, and developed pressure, with a transient increase in diastolic pressure. The nadir of the relative decrease in $LVdP/dt_{max}$ was less extreme in the moderate contusion group than in the severe contusion one ($-18 \pm 12\%$ *vs.* $-42 \pm 17\%$; $P = 0.002$; fig. 2). The decrease in $LVdP/dt_{max}$ remained significant throughout the observation period in the severe contusion group ($-27 \pm 16\%$ at the end of the period); all the hemodynamic parameters rapidly returned to basal values in the moderate contusion group (table 1, fig. 2).

The CK_{tot}, LDH_{tot}, and cTnI values were increased in the effluent of the preparations in the contusion groups compared with the control group (fig. 1). Peak values of CK_{tot} (67 ± 48 *vs.* 51 ± 34 $U \cdot l^{-1} \cdot g^{-1} \cdot min^{-1}$) and AUC_{CK} (6,570 ± 5,133 *vs.* 5,639 ± 3,375 U/g) were similar in the two contusion groups. In contrast, peak values of LDH_{tot} (18 ± 11 *vs.* 7 ± 4 $U \cdot l^{-1} \cdot g^{-1} \cdot min^{-1}$) and AUC_{LDH} (1,940 ± 1,332 *vs.* 789 · 493 U/g) were higher in the severe contusion group than in the moderate contusion group. In the same way, peak values of cTnI (1.74 ± 1.03 *vs.* 1.22 ± 0.83 $\mu g \cdot l^{-1} \cdot g^{-1} \cdot min^{-1}$) and AUC_{cTnI} (475 ± 353 *vs.* 237 ± 136 $\mu g/g$) were higher in the severe contusion group than in the moderate contusion group. Compared with the moderate contusion and control groups, cTnI remained signifi

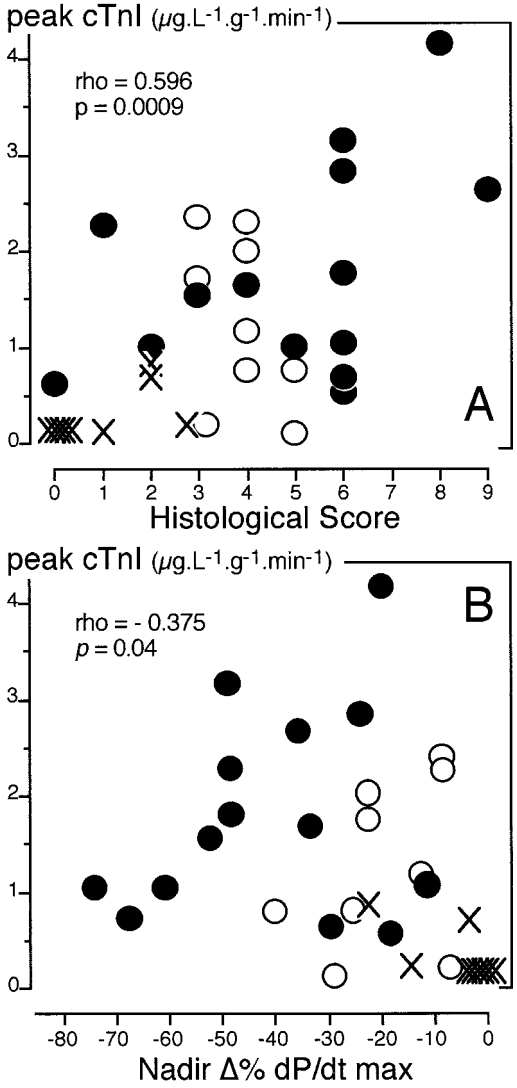

Fig. 3. Relationships between the peak values of cardiac troponin I concentration (cTnI) in the effluent of the preparations and the anatomic injury (histologic score; *A*) and the nadir of the decrease in left-ventricular function ($LVdP/dt_{max}$; *B*) in the three groups during the observation period.

cantly elevated at the end of the observation period in the severe contusion group, giving a biphasic shape to the concentration mean curve of cTnI (fig. 1).

The nadir of the decrease in $LVdP/dt_{max}$ was correlated negatively with the anatomic injury ($\rho = -0.467$, $P = 0.009$). As shown for cTnI in figure 3, peak values of CK_{tot} ($\rho = 0.491$, $P = 0.006$), LDH_{tot} ($\rho = 0.594$, $P = 0.001$), and cTnI ($\rho = 0.596$, $P = 0.0009$), as well as AUC_{CK} ($\rho = 0.496$, $P = 0.008$), AUC_{LDH} ($\rho = 0.607$, $P = 0.001$), and AUC_{cTnI} ($\rho = 0.512$, $P = 0.006$), were correlated significantly with the anatomic injury. Peak cTnI ($\rho = -0.375$, $P = 0.04$; fig. 3) and AUC_{LDH} ($\rho = 0.429$, $P = 0.021$) values were correlated negatively with the nadir of the decrease in $LVdP/dt_{max}$.

Discussion

The present study demonstrates that after an experimental global cardiac blunt trauma, the histologic lesions of myocardial injury were similar to those observed after a severe ischemic stress; the extent of contusion was correlated with cardiac dysfunction and well estimated by the amount of cTnI release.

An alteration of ventricular function was common after blunt cardiac trauma[18] and usually could be attributed to the extent of myocardial crushing or the consequences of a decrease in myocardial oxygen supply caused by a vascular injury. The present correlation between the decrease in LVdP/dtmax and the extent of myocardial injury is in agreement with an anatomic hypothesis that was described previously in an experimental closed chest model of cardiac injury.[19] The histologic lesions, however, especially the contraction bands, may result from ischemia–reperfusion consequences through secondary ionic abnormalities.[20] In an open-chest swine model of cardiac trauma, a transient redistribution of coronary blood flow from endocardium to epicardium was demonstrated in the injured region; a global increase in coronary blood flow was noted in the nontraumatized parts of the heart.[21] The contribution of an ischemic injury to the posttraumatic cardiac dysfunction is supported further by the fact that a local anesthetic drug, lidocaine, markedly improved the contusion-related decrease in contractility in the present experimental model.[14] Such a beneficial effect of lidocaine has been reported after myocardial hypoxia[22] and attributed to the membrane-stabilizing action[23] or the interference with cationic movements of the drug.[24] The present study suggests that the amount of circulating cTnI reflects the anatomic extent and functional consequence of a traumatic cardiac injury, as previously reported after a human myocardial infarction.[25]

Isolated heart preparations without recirculation of the buffer commonly are used to assess the biochemical patterns of myocardial ischemic stress, because the local degradation of markers is unlikely,[26] the timed collection of effluent samples provides indirect information on the tissue status,[27] and the direct access to the coronary circulation prevents a dilutional influence of peripheral blood samples in a whole animal. The present study extended the use of isolated heart models to the evaluation of the biochemical consequences of cardiac trauma. Levels of both cardiac enzymes and cTnI demonstrated early and similar increases after the blow. This pattern may correspond to the release of the cytosolic content of enzymes and unbound contractile proteins through an abnormal cellular membrane. After a limited cardiac injury (moderate contusion), the release of cardiac markers ceased rapidly and activities or concentrations returned to the baseline values at the end of the observation period. After a severe contusion, in contrast with CK_{tot}, a sustained release of cTnI was observed concomitantly with the prolonged ventricular dysfunction, despite a restored coronary blood flow.[15] Such a differential biochemical pattern was observed after ischemia and reperfusion in a similar experimental model[28] and attributed to a proteolytic degradation of myofibrils leading to the liberation of a cytosolic fraction.[29] A difference between the time courses of CK_{tot} and LDH_{tot} has been reported after hypoxia or ischemia;[28] the latter seemed to have a greater informative value than the former concerning the severity of myocardial injury in the present study. Considering the role of altered regulatory proteins in cardiac contractile dysfunction after myocardial ischemia,[27,30] the circulating levels of cTnI after blunt cardiac trauma might reflect both the extent of myocardial crushing and the severity of myocardial ischemia. Ultimately, structural analysis of cTnI would be useful to assess the relative importance of mechanic and ischemic injuries as well as the severity of hemodynamic impairment after blunt cardiac trauma.[30,31]

Cardiac enzymes are irrelevant for the diagnosis of myocardial damage in trauma patients, because of the peripheral rhabdomyolysis.[9,10] The level of the MB isoenzyme of CK is not correlated with the posttraumatic decrease in cardiac output.[32] The cardiospecificity of the protein supports the diagnostic value of cTnI for myocardial damage after cardiac trauma.[12,13] Considering the prolonged release of the protein, a retrospective diagnosis of blunt cardiac injury seems possible during the first

posttraumatic days. If the risk of posttraumatic cardiovascular complications is related to the amount of myocardial damage, cTnI might fill clinical need for a valuable predictive indicator.

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