EXPERIMENTAL STUDIES

Increased Intracranial Pressure Elicits Hypertension, Increased Sympathetic Activity, Electrocardiographic Abnormalities and Myocardial Damage in Rats

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Intracranial pressure was increased in 59 rats by inflating a subdural balloon to a total mass volume of 0.3 ml. The increase in intracranial pressure ranged from 75 to >500 mm Hg. With few exceptions, mean arterial pressure increased to as high as 227 mm Hg during the increase in intracranial pressure. Significant increases in plasma catecholamines, major electrocardiographic changes and a considerably shortened survival time were observed only in the rats that demonstrated an increase in mean arterial pressure >50 mm Hg. A perfusion study with liquid silicone rubber (Microfil) revealed dilated irregular myocardial vessels with areas of focal constriction consistent with microvascular spasm. Histologic examination of the myocardium revealed widespread patches of contraction band necrosis and occasional contraction bands in the smooth muscle media of large coronary arteries.

These observations suggest that myocardial damage after suddenly increased intracranial pressure resulted both from exposure to toxic levels of catecholamines and from myocardial reperfusion. Extension of these studies to humans suggests that a detailed assessment of myocardial function should be performed in victims of severe brain injury. Myocardial dysfunction may be a major determinant of the patient’s prognosis or may render the heart unsuitable for transplantation.

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myocardial damage. Myocardial necrosis and subendocardial hemorrhage have been described in humans after intracranial injury, particularly subarachnoid hemorrhage, and in experimentally induced intracranial hemorrhage in animals (26-34). The frequency of the cardiac damage appears to be increased when the intracranial disorder is accompanied by a sudden increase in intracranial pressure (8,9). Biochemical evidence suggesting damage to the heart has also been reported to accompany sudden intracranial events. Elevated serum levels of creatinine kinase and its myocardial isoenzyme have been observed in patients suffering from subarachnoid hemorrhage, stroke and other cerebral disorders (35-38).

Myocardial dysfunction may be a major determinant in the prognosis of these patients. Victims of brain death are also potential donors for cardiac transplantation; cardiac damage in such a circumstance may render these hearts unusable or, if damage escapes detection, these hearts when transplanted may develop unexpected cardiac dysfunction.

To further clarify our understanding of the effects of increased intracranial pressure, we designed a model of sudden intracranial hypertension in rats with use of a subdural balloon. In this study, we examine the hemodynamics, ECG, plasma catecholamines and cardiac pathology exhibited by this paradigm. Our results provide new insight into the pathophysiology of cardiovascular injury after brain trauma.

**Methods**

**Experimental preparations.** Short-term experiments were carried out on a total of 88 male white Wistar rats weighing between 350 and 450 g. Sixty-seven rats, of which 8 served as controls, were used for the cardiovascular study. Twenty-one rats, of which 9 served as controls, were used for the Microfil perfusion study. The rats were anesthetized with 10% saline solution of alpha-chloralose (75 mg/kg) and urethane (525 mg/kg) intraperitoneally. The right femoral artery was cannulated (PE 50 catheter) for recording systemic blood pressure and obtaining blood samples; the femoral vein was cannulated for drug administration.

After tracheotomy was performed, the rats were paralyzed with intravenous pancuronium bromide (1.2 mg/kg) and supplemental intravenous injections (0.8 mg/kg) were administered at 45 min intervals to maintain paralysis. The animals were artificially ventilated with a mixture of 80% room air and 20% oxygen (O
2) with a Harvard-680 Rodent Respirator. During the course of the experiments, appropriate adjustments were made to maintain pH and blood gases at physiologic values (pH 7.34 to 7.44, partial pressure of carbon dioxide (PCO
2) 30 to 40 mm Hg and O
2 >90 mm Hg) (Radiometer BMS-Mk2 Blood Micro System). Each rat was then laid on its abdomen and its head was held securely in a head holder.

**Induction of intracranial hypertension.** A midline scalp incision was made extending from the coronal suture to the lambdoid suture, and the muscles were retracted to expose the calvarium. One burr hole was drilled 2 mm lateral to the sagittal suture on both sides, approximately 7 mm posterior to the orbits. The holes were drilled so that their diameters were sufficient to allow snug placement of the catheters described later. The dura mater was carefully opened, and a flow of cerebrospinal fluid was assured to allow easy placement of the catheters in the subdural space.

**Intracranial pressure was measured** by way of a PE 50 catheter inserted through the right burr hole and placed over the right parietal lobe. Intracranial pressure was increased by means of a 3F Fogarty arterial embolectomy catheter (Edwards Laboratories Inc., model 12-040-3F), which was placed subdurally over the left parietal lobe. To prevent leakage of cerebrospinal fluid from around the catheters, the burr holes were tightly sealed with Fleck's Zinc Cement (Mizzy, Inc.).

**After the surgical manipulations were completed,** the animals were left undisturbed for 20 min to attain steady state before proceeding with the experiments. The intracranial pressure was then increased by inflating the balloon of the catheter with distilled water to a total mass volume of 0.3 ml. The injection was performed in a consistent manner over a period of 2 s by means of a tuberculin syringe mounted on a spring-loaded automatic injector. Elevated intracranial pressure was maintained for 15 s, after which the balloon was deflated abruptly. Blood samples were taken at various time intervals to determine plasma catecholamine concentrations, which were measured radioenzymatically by the method of Sole and Hussen (39) with modifications (40).

In the eight control rats only a scalp incision was made without any catheters implanted in the cranium or burr holes drilled. However, the rest of the surgical procedures were as described previously for the traumatized rats. All experiments were approved by the University of Toronto Animal Care Committee and conformed to the American Heart Association Guidelines on research animal use.

**Pressure and ECG monitoring.** Intracranial pressure and arterial pressure were recorded during the course of the experiments with Bell and Howell physiologic pressure transducers type 4-327-1. Continuous ECG recordings were made of standard lead I from subcutaneous needle electrodes. Heart rate was assessed manually from the RR intervals. The recording ECG needles and the pressure transducers were all connected to a Hewlett-Packard 7758A multichannel recorder.

**Microfil perfusion study and histology.** To study the cardiac microcirculation, 12 additional rats underwent the experimental procedures as mentioned previously with the addition of the left brachial artery cannulation with a PE 50 catheter. Immediately after the intracranial pressure was released by balloon deflation, the animals received through
the brachial artery 2 ml heparinized saline solution (20 units/mI) followed by hand injection, at a steady rate at approximately 100 mm Hg, of 5 ml of liquid yellow silicone rubber (Microfil: Canton Bio-Medical Products). Microfil is a liquid that perfuses the arterial and venous circulation and hardens within minutes, maintaining the shape of the vasculature. The hearts continued to beat for approximately 1 min during the procedure. The Microfil was prepared just before the injection by mixing together 3 parts of the thinner, 2 parts of the silicone rubber and 5% of the above volume of hardener. After the perfusion, the hearts were excised and placed in 3.7% buffered formaldehyde.

Control hearts perfused with Microfil were obtained from nine rats undergoing similar experimental procedures except for the cranial manipulations.

After 2 to 4 weeks of fixation, tissues were sectioned. The heart was sliced into rings 2 to 3 mm thick from apex to base. Random slices of brain, lung and kidney were prepared. The brain tissue included the traumatized area adjacent to the balloon if present. One-half of the sections from each organ were embedded in paraffin and were processed routinely for light microscopy. Paraffin sections were stained with hematoxylin-eosin and were evaluated for the presence of necrosis (contraction bands or hyper eosinophilia, or both, in the heart; traumatic disruption in the brain), hemorrhage (heart, brain, lungs) and edema (lungs). The remaining tissues were “cleared” by the method of Schaper (41) to evaluate the microcirculation. This method leads to semitranslucent parenchyma with the silicone rubber-filled vessels standing out against a clear background. Vessels in all organs were analyzed for the presence of constrictions (spasm), dilations, tortuosity or aneurysms as described previously (42-44).

Calculations and statistics. Differences among groups for the studied variables were evaluated by the one way analysis of variance. If the test was significant (p < 0.05) the Neuman-Keuls test was employed (p < 0.05) for multiple comparisons. The log rank test was utilized to determine differences in survival rate among groups in the life table. Mean arterial pressures were calculated as the diastolic pressure plus one third the pulse pressure. The results are presented as mean values ± SE.

Results

Intracranial pressure response. The level of elevation of the intracranial pressure in response to the inflation of the subdural balloon to a standard mass volume of 0.3 ml varied widely in the 59 rats (Table 1). With the exception of two animals, the intracranial pressure increased above basal diastolic blood pressure. However, even in these two rats, hemodynamic responses similar to those in the other rats were observed, although intracranial pressure increased to only 70% and 90% respectively, of the basal diastolic pressure. The peak height of intracranial pressure occurred at 2 s from the onset of balloon inflation. During the 15 s of balloon inflation intracranial pressure decreased gradually but never fell below diastolic pressure. However, as soon as the balloon was deflated, intracranial pressure declined to baseline levels (0 to 5 mm Hg). The reflex responses described next did not depend on the height of intracranial pressure during inflation.

Blood pressure changes. The increase in intracranial pressure stimulated an immediate increase of blood pressure in 30 (85%) of the rats to levels as high as 280/200 mm Hg. There was no correlation between these two variables. The remaining rats, regardless of the increase in intracranial pressure, exhibited a decrease in blood pressure.

To determine whether there was some association between blood pressure changes, catecholamines and survival time, the animals were categorized into three groups according to the blood pressure change they exhibited in response to increased intracranial pressure.

Group 1: 9 rats that developed a decrease in blood pressure.

Group 2: 9 rats that developed only minor elevations of blood pressure, the difference between baseline and peak mean arterial pressure being ≤ 30 mm Hg.

Group 3: 41 rats that developed a change between baseline and peak mean arterial pressure > 50 mm Hg.

In groups 1 and 2 the only significant change (p < 0.01) of mean arterial pressure from baseline (group 1, 120 ± 6 mm Hg; group 2, 132 ± 6 mm Hg) was evident during the time of elevated intracranial pressure (group 1, 82 ± 9 mm Hg; group 2, 166 ± 8 mm Hg). Soon after the release of the balloon, mean arterial pressure returned to baseline levels. In group 3 a different response was observed; mean arterial pressure peaked significantly (p < 0.01) during elevated levels of intracranial pressure (basal mean arterial pressure 125 ± 4 mm Hg, peak 198 ± 2). However, after the release of intracranial pressure, blood pressure dropped significantly (p < 0.01) below baseline levels. This decline progressed until the rats went into shock and were euthanized.

Heart rate. The rats either did not show any change in heart rate (basal heart rate = 459 ± 5 beats/min) or developed transient increases of < 10% that, although statistically significant, were physiologically trivial.

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<th>Table 1. Intracranial Pressure Response to 15 s of Balloon Inflation to Mass Volume of 0.3 ml in 59 Rats</th>
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Electrocardiographic abnormalities. An analysis of the ECG revealed abnormalities in the ST-T wave pattern and in the cardiac rhythm in the brain-injured rats. These changes were evident during injury and persisted for 2 to 5 min after injury; a very few of the rats exhibited some minor ECG alterations lasting ≤10 min.

The response fell into three major categories: 21 (35%) of the 59 brain-traumatized rats did not show any ECG alterations; 14 (24%) exhibited minor changes consisting of slight T wave changes, occasional atrial premature beats or a single isolated ventricular premature beat; the remaining 24 rats (41%) manifested a combination of many abnormalities that were considered to be serious. The most common arrhythmias seen were multiple ventricular couplets, multifocal ventricular premature beats or ventricular tachycardia. These changes were often accompanied by ST elevations and T wave inversion.

Relation between changes in mean arterial pressure and electrocardiographic abnormalities. The traumatized rats with mean arterial pressure changes of <50 mm Hg in response to increased intracranial pressure (groups 1 and 2) did not exhibit any serious ECG changes. Fifteen of these 18 rats had no changes in the ECG, the remaining 3 displayed minor changes. However, when changes in mean arterial pressure were >50 mm Hg (group 3), 24 of 41 animals manifested serious ECG changes, 11 showed minor changes and only 6 had a normal ECG.

Catecholamine response. To assess the activity of the sympathetic nervous system, plasma catecholamines were measured. Mean catecholamine levels before the elevation of intracranial pressure were 827 ± 56 and 373 ± 43 pg/ml for norepinephrine and epinephrine, respectively. These concentrations rose to peak levels as high as 9,090 pg/ml for norepinephrine and 20,379 pg/ml for epinephrine in individual animals. Because the rise of norepinephrine correlated significantly with that of epinephrine (r = 0.87, p < 0.01), and an analysis of their responses separately was not more informative than an analysis of their sum, total catecholamine levels representing the pooled sum of both will be reported.

Figure 1 illustrates plasma catecholamine concentrations at different time intervals. The maximal catecholamine concentrations were found at approximately 30 s after the release of intracranial pressure when the first sample was taken after increasing the intracranial pressure. This peak, which was highly significant (p < 0.01) and pronounced, was found only in group 3 (>50 mm Hg increase in mean arterial pressure). Within 5 min, the level dropped and analysis of variance failed to detect any changes between baseline and samples taken at any time other than the 30 s sample. Even though there appeared to be a slight early increase in catecholamines in groups 1 and 2 (a decrease or only a minor change in mean arterial pressure), the changes at all time intervals were not significantly different from baseline and control levels.

Figure 2 clearly indicates that the catecholamine concentrations in the 14 rats with minor and the 24 rats with serious ECG changes were markedly higher than in the 21 rats with no ECG changes and the 8 control rats (p < 0.01).

Relation between peak mean arterial pressure and catecholamine concentrations (Fig. 3). It was observed that for levels of plasma catecholamine <3,500 pg/ml, mean arterial pressure correlated significantly with increasing catecholamines (r = 0.62, p < 0.01) (Fig. 3, inset). Increases in plasma catecholamines >3,500 pg/ml were not accompanied by any further increases in blood pressure.
Survival (Fig. 4 and 5). The 59 rats exhibited three different patterns of survival. Thirty-one rats (58%) developed cardiovascular shock and became severely hypotensive within 5 min of the trauma and died; they were considered to have had sudden death. Seventeen rats (29%) were able to maintain normal blood pressure for periods >5 min but died of cardiovascular shock within 1 h; these were termed short-term survivors. The remaining 11 rats (19%) maintained a normal blood pressure and ECG, and were killed at the end of the 3 h period; they were termed long-term survivors.

It is evident from Figure 4 that markedly high levels of blood pressure and catecholamines were associated with shortened survival time. Survival time was also shortened with increasing ECG abnormalities (Fig. 5). The life table for normal, minor and serious ECG changes showed that at 3 h the survival rates were 35% for normal, 18% for minor and 5% for serious ECG changes. The log rank test revealed a significant difference in the survival rate of the three groups ($\chi^2 = 5.865, p < 0.05$).

**Microfil Perfusion Study**

Cardiovascular response. Eleven of the 12 rats with brain trauma that underwent Microfil perfusion experienced an increase in intracranial pressure >500 mm Hg; 8 of these rats exhibited a change in mean arterial pressure >50 mm Hg. With the exception of one animal, all those with a mean arterial pressure change >50 mm Hg had serious ECG abnormalities. These changes consisted of multiple occurrences of ventricular couplets, ventricular premature beats and tachycardia and were usually accompanied by ST elevation and T wave inversion. Only one of the 4 four rats with a change in mean arterial pressure <50 mm Hg had serious ECG changes, 2 had minor changes and one showed no alteration. The changes that were considered to be minor included slight T wave changes or a single isolated atrial or ventricular premature beat. All 12 rats manifested pathologic changes in the heart.

**Histology.** The myocardial lesions found with hematoxylin-eosin staining consisted mainly of contraction band necrosis (Fig. 6A) and were present in 11 (92%) of the 12 brain-injured rats. The necrosis was not localized to one particular region but was dispersed predominantly in the subepicardium, the midwall of the left ventricle and the interventricular septum. Three of the 12 rats also manifested smooth muscle contraction bands in the media of the coronary arteries (Fig. 6B). Eight of the 12 hearts showed diffuse...
Figure 6. A, An area of acute myocardial necrosis in a traumatized rat. The region above the thick arrows is congested and hyper eosinophilic. Many myocardial cells demonstrate contraction band necrosis (thin arrows) characteristic of reperfusion injury related to vascular spasm or a high level of catecholamines. B, An intramyocardial coronary artery from a traumatized rat demonstrates medial smooth muscle disorganization and focal smooth muscle hyper eosinophilia consistent with contraction bands (arrows). The dark intraluminal mass is silicone rubber that has retracted as a result of paraffin embedding. Around the vessel, the myocardium exhibits focal contraction band necrosis (CB). (A and B, hematoxylin-eosin; ×400, reduced by 30%).

and severely congested vessels; of these, 4 showed disorganized coronary artery smooth muscle cells in the vascular wall. One heart exhibited smooth muscle vacuolization and disorganization. There was one case of subepicardial hemorrhage and another case of vascular smooth muscle necrosis associated with perivascular hemorrhage and edema.

In contrast, only two (22%) of the nine control animals manifested myocardial contraction band necrosis, but these were isolated and rare lesions. Another two exhibited diffuse vascular congestion, but vascular lesions were not observed. None of these control animals manifested ECG changes.

The brains of all 12 traumatized rats showed severe pathologic changes. Multiple subarachnoid, periventricular and cortical hemorrhage without tissue necrosis was seen in five rats. Extensive tissue necrosis and traumatic disruption with associated hemorrhage were observed in the remaining seven rats, and in three of these, the lesions were particularly severe (Fig. 7). The control brains were normal.

No differences were observed between the lungs of control and traumatized animals. Both groups had focal areas of pulmonary edema or intra-alveolar hemorrhage, or both. One traumatized rat had acute fibrin-platelet thrombi in peribronchial vessels. The kidneys were histologically normal in both groups.

Microvascular pathology. The cardiac microvasculature from the traumatized animals was markedly abnormal in 7 of the 10 rats in which perfusions were adequate for analysis.

Figure 7. A portion of rat brain with changes consistent with severe trauma. There are multiple intraparenchymal hemorrhages and tissue disruption (hematoxylin-eosin; ×60, reduced by 30%).
These rats had multiple constricted lesions consistent with spasm, in addition to areas of dilation and microvascular irregularity (Fig. 8A). Paradoxically, three rats with the most severe head trauma had essentially a normal-appearing microcirculation. However, these three rats had extensive multifocal myocardial damage and histologic lesions in the large epicardial coronary arteries consisting of medial disorganization and contraction bands (Fig. 6B). Microfil perfusion studies revealed essentially normal vessels in the control hearts (Fig. 8B). One rat had rare constrictions in the coronary microcirculation, whereas four of nine rats showed some isolated focal dilations.

The cerebral microvasculature was generally decreased or absent in areas of hemorrhage and tissue disruption. Peripheral to these areas, focal spasm, irregularity and coiling were noted in the microcirculation (Fig. 9). Control cerebral vessels were generally normal. Analysis of perfused lungs and kidneys from traumatized and control rats demonstrated no difference between the groups.

Discussion

Blood pressure response to increased intracranial pressure.

The technique of increasing intracranial pressure by means of an epidural balloon has been used in dogs, monkeys and cats (3, 10, 45, 46). As in the present study, these investigations showed that elevated intracranial pressure can alter cardiovascular homeostasis. Although extreme increases in intracranial pressure are not needed to elicit the response, there is a threshold below which this response could not be provoked. This threshold has been described as the diastolic blood pressure (47), the systolic blood pressure (1, 3) or the mean blood pressure (48, 49). We found that increases in intracranial pressure above diastolic pressure in the rat usually, but not invariably, elicited hypertensive responses of various degrees of intensities, although the heart rate was unchanged or slightly increased.

Mechanisms of the vasopressor response. Different mechanisms have been proposed to explain this vasopressor response to increased intracerebral pressure including ischemia of the medullary vasomotor center, direct compression of the brain or axial distortion of the brainstem (1, 3, 50, 51).
Although discussion of the exact mechanism is beyond the scope of this study, it has been suggested that the neural pathways involved probably exert their effects through activation of the sympathoadrenal system initiated in the hypothalamus by the increased intracranial pressure (29,47). It has been demonstrated that electrical stimulation of the hypothalamus, subthalamus or the stellate ganglia can produce ECG abnormalities, an increase in heart rate and vasoconstriction with an elevation in blood and pulse pressure (15,52-57). These responses can be abolished or markedly inhibited by beta-adrenergic blockade with propranolol, C2 spinal section, clonidine (a centrally acting alpha-adrenergic agonist that reduces sympathetic efferent nerve traffic) or by chemical sympathectomy and bilateral adrenalectomy (15,16,47,58,59).

**Plasma catecholamines.** An increase in sympathoadrenal tone may be reflected by alterations in plasma catecholamines. Immediately after the increase in intracranial pressure in our studies, plasma catecholamines were elevated markedly similar to observations in other animal models and humans (6,7,10-13). This increase in catecholamines was accompanied by increases in blood pressure, abnormalities in the ECG and shortened survival time.

**Mechanisms of cardiac damage and ECG changes.** The rats with the greatest increases in blood pressure and plasma catecholamines had a higher incidence of ECG abnormalities and a shorter survival time. Although it is possible that the presentation of a sudden pressure load to the left ventricle could have contributed to myocardial damage, as manifested by the ECG, leading to premature death, the present study also implicates an important pathogenetic role for centrally stimulated catecholamine release. Cardiac injury was confirmed by our Microfil studies, which are the first to demonstrate marked changes in perfusion at the microcirculatory level. The presence of dilated irregular vessels with focal areas of constriction is consistent with microvascular spasm. The demonstration of microvascular spasm and the appearance of focal segmental areas of myocardial necrosis with hemorrhage and congestion suggest reperfusion-induced myocardial injury. The paradox of a relatively normal cardiac microcirculation in three rats with severe cerebral trauma and extensive myocardial lesions can be explained by changes induced in the epicardial coronary arteries supplying larger areas of myocardium. Histologic features of smooth muscle medial disorganization and contraction bands in these vessels suggest that coronary spasm may have occurred in these animals (60); this type of change has been identified in postmortem human coronary arteries and is thought to be induced by catecholamines (60).

**Toxic catecholamine effect on myocardium.** The presence of contraction band necrosis in the cardiomyocytes of traumatized animals suggests that a direct toxic effect of the marked catecholamine increase on myocardial cells may also be of pathogenic importance. Myocardial necrosis has also been readily produced experimentally by the parenteral administration of catecholamines (61-64) or by direct stimulation of the stellate ganglia (57,65). Similar cardiac damage may result from electrical stimulation of specific regions of the brainstem and hypothalamus known to increase sympathetic discharge (66,67), but not after repeated stimulation of brain areas with little autonomic function such as the thalamus and the parietal lobe (67). Although cardiac damage may be the result of high circulating levels of catecholamines, injury may also be due to massive release of norepinephrine at local cardiac sympathetic nerve terminals; for example, Reichenbach and Benditt (64) observed that sympathetic nerve terminals, adjacent to regions of myofibrillar degeneration, exhibited a marked reduction in catecholamine-containing granules.

**Effect of pharmacologic agents.** The importance of sympathetic efferent outflow for the mediation of cardiac damage after brain injury has been demonstrated in several pharmacologic studies. Hunt and Gore (32) analyzed hearts of mice subjected to intracranial hemorrhage with and without propranolol pretreatment. They observed a reduction in myocardial damage from 46% in the untreated group to 18% in the treated animals. Reserpine, a drug that depletes tissue catecholamines by interfering with their uptake and storage, appears to offer similar protection (30,31). Although this evidence suggests that massive catecholamine release is important in the pathogenesis of myocardial damage after brain injury, it is possible that other neurohumoral mechanisms for example, renin-angiotensin system, insulin may also contribute.

**Conclusions and clinical implications.** Systemic hypertension, a minor increase in heart rate, abnormalities in the myocardial vasculature and widely distributed focal areas of myocardial damage, particularly contraction band necrosis, are associated with suddenly increased intracranial pressure in the rat. It appears likely that transient but massive sympathoadrenal activation, perhaps initiated in the hypothalamus by the increased intracranial pressure, may be a significant contributor to both the pressor response and the myocardial damage. If these observations are relevant to patients suffering from acute brain injury due to trauma or other lesions such as spontaneous intracranial hemorrhage, they would suggest that, by the time such patients receive medical attention, evidence for acute hypertension and "sympathetic storm" may no longer be present although substantive myocardial damage may exist. An assessment of these patients should take such a possibility into account and consideration should be given to various therapeutic strategies that might ameliorate these effects or prevent further damage. Furthermore, a detailed assessment of myocardial function should be performed in injury victims who are potential donors for cardiac transplantation.
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References


