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Original Article

Evaluation of cerebral-cardiac syndrome using echocardiography in a canine model of acute traumatic brain injury

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Abstract: Previous studies have confirmed that traumatic brain injury (TBI) can induce general adaptation syndrome (GAS), which subsequently results in myocardial dysfunction and damage in some patients with acute TBI; this condition is also termed as cerebral-cardiac syndrome. However, most clinicians ignore the detection and treatment of myocardial dysfunction, and instead concentrate only on the serious neural damage that is observed in acute TBI, which is one of the most important fatal factors. Therefore, clarification is urgently needed regarding the relationship between TBI and myocardial dysfunction. In the present study, we evaluated 18 canine models of acute TBI, by using real-time myocardial contrast echocardiography and strain rate imaging to accurately evaluate myocardial function and regional microcirculation, including the strain rate of the different myocardial segments, time-amplitude curves, mean ascending slope of the curve, and local myocardial blood flow. Our results suggest that acute TBI often results in cerebral-cardiac syndrome, which rapidly progresses to the serious stage within 3 days. This study is the first to provide comprehensive ultrasonic characteristics of cerebral-cardiac syndrome in an animal model of TBI.

Keywords: Traumatic brain injury, real-time myocardial contrast echocardiography, strain rate imaging, myocardial ischemia, cerebral-cardiac syndrome

Introduction

Acute traumatic brain injury (TBI) often leads to neurohormonal disorders that induce cerebral-cardiac syndrome, which is characterized by acute myocardial damage [1], myocardial ischemia, and heart failure [2, 3]. Because neural damage is usually an urgent and serious condition, abnormal cardiac function is easily ignored in clinical practice, and tends to be one of the most important fatal factors in cases of acute TBI. However, the cardiac symptoms are occasionally mild in TBI patients, or may only manifest as slight palpitations and chest discomfort, which is not always identified in the patients' complaints. Moreover, abnormalities are not always observed during clinical examinations in the early stage [4]. Therefore, it is necessary to further clarify the relationship between TBI and cardiac dysfunction.

To date, only a few studies have quantifiably evaluated cerebral-cardiac syndrome by ultrsonography in animal TBI cases, because of the variable injury standards and difficultly involved in the emergency treatment of TBI. To attain consistent and reliable data, the current study used real-time myocardial contrast echocardiography (RTMCE) and strain rate imaging (SRI) to accurately evaluate the extent of cerebral-cardiac syndrome in a canine model of TBI.

Materials and methods

Animal samples

Twenty healthy male and female mongrel dogs were used in this study. The body weight range was 14-20 kg (mean, 16.06 ± 2.08 kg).

Imaging methods

We used a GE Vivid 7 color ultrasound system (GE Company, USA) that was equipped with a 2.5-MHz probe and a system for contrast echocardiography and strain measurements. The

Table 1. Myocardial contrast echocardiography results for the injured mongrel dogs before and after injury

Detection time	A	β	A·β
Pre-injury	31.55 ± 6.56	1.20 ± 0.60	37.17 ± 10.36
6 h after injury	29.35 ± 5.82	1.11 ± 0.70	35.65 ± 9.22
1 day after injury	19.23 ± 8.76*	0.83 ± 0.23*	18.56 ± 6.68*
3 days after injury	13.87±6.46*	0.73 ± 0.35*	13.78 ± 5.33*

*Compared to results before and 3 h after the injury, $P < 0.05$. Data are presented as mean ± standard deviation.

upper surface of the right temporal lobe in all the mongrel dogs was set to be the center of focus, within an area of 5 cm × 5 cm. The blast injury was induced using 1 g of trinitrotoluene and the blast source had a diameter of 10 mm [5]. A new ultrasound contrast agent (SonoVue) was applied during the RTMCE imaging and SRI of the animal models at 6 h, 1 day, and 3 days after the injury.

The evaluated parameters included the myocardial motion velocities of the interventricular septum as well as those of the anterior, posterior, lateral, and inferior walls of the left ventricle along the short axis. The strain rate along the long axis and time-density curve variables that were acquired after myocardial reperfusion included myocardial imaging strength during the plateau phase (A), the average slope of the increasing reperfusion curve (β), and the regional myocardial blood flow (A·β).

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL) was used for all statistical analyses. Data are expressed as mean ± standard deviation, and differences between the groups were assessed using the Paired *t*-Test. *P*-values of < 0.05 were considered statistically significant.

Results

Establishing animal models

Based on the standard dog model of acute TBI, we successfully created 18 models in this study. Among these animals, 1 died at 10 h after the injury, 2 died after 1 day, and 15 survived until 3 days after the injury.

RTMCE results before and after the injury

A total of 50-70 images that were recorded after ultrasonic destruction of the microbubbles were selected, and 2-5 regions of interest (their size was consistent with inner end-diastolic wall thickness) were selected based on the extent of the lesion. Compared to those before the injury, the post-injury levels of A, β, and A·β decreased significantly in 4 myocardial segments of the anterior and inferior left ventricle wall in 3 mongrel dogs at 6 h. At 1 and 3 days after the injury, the levels of A, β, and A·β decreased significantly in 29 myocardial segments, compared to the pre-injury values ($P < 0.05$; **Table 1**, **Figure 1**).

Myocardial strain rate for each segment before and after the injury

Before the injury, the systolic longitudinal strain rates were negative along the long axis, and the color coding revealed that the tone transitioned from yellow to red for increasingly negative strain rates. In the same direction, the diastolic strain rates were positive, and the tone transitioned from cyan to blue for increasingly positive strain rates. The 3 major peaks in the strain rate-time curve (i.e., the S, E, and A peaks) had clear outlines. The color of each injured myocardial segment gradually decreased from 6 h to 3 days after the injury, and exhibited irregular variations. The color in a few segments was pure green, and the strain rate-time curve lost its normal shape and exhibited an irregular outline (**Figure 2**).

The crests of the S, E, and A peaks were very small and subsequently disappeared, and the peak values were significantly lower than those obtained before the injury ($P < 0.05$, **Table 2**).

Discussion

Acute brain injury is followed by different levels of cerebral edema, which suppress and displace brain circulation; consequently, the increased intracranial pressure can directly or indirectly affect the hypothalamus and brain stem. Unfortunately, hypothalamic dysfunction-induced autonomic dysfunction can result in sympathetic-adrenal medulla abnormalities and increased catecholamine release. The excess catecholamine can then travel from the adrenergic nerve endings in the heart to the myocardia, and cause focal dissolution, cardiomyocyte necrosis, and changes in the contrac-

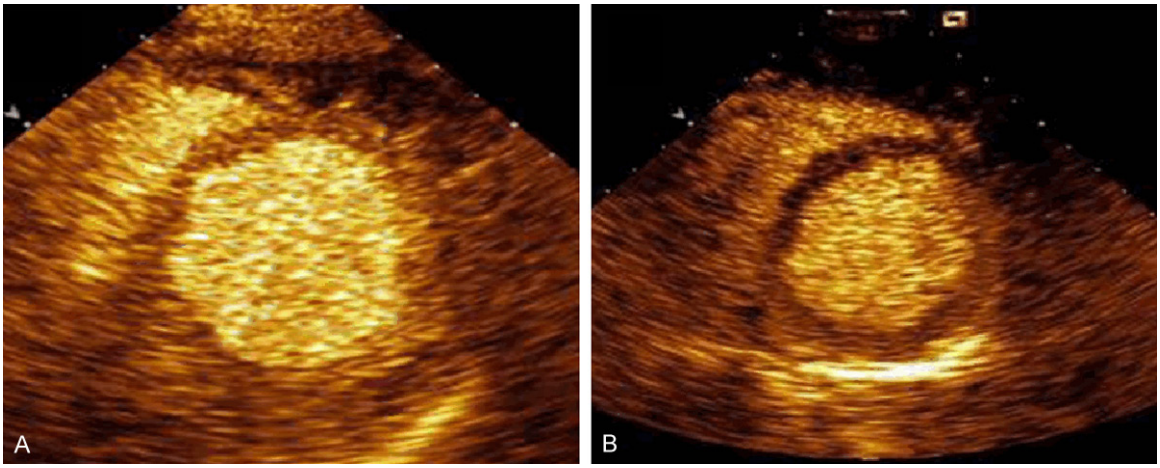

Figure 1. Short-axis imaging of the left ventricle: anterior myocardial perfusion was significantly reduced at 3 days after the injury, compared to that before the injury. (A) Ultrasonic image recorded before TBI, (B) Images of 3days after TBI.

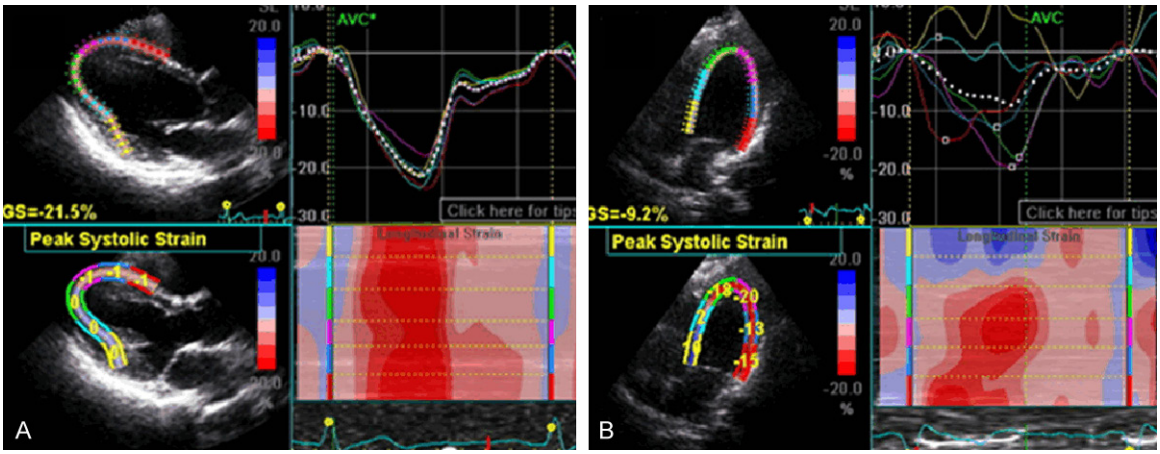

Figure 2. Long-axis imaging of the left ventricle at 1 day after the injury: no variations are observed in the color of the regional myocardium, and the strain rate-time curve is disordered (A) strain rate recorded before TBI, (B) images of 1day after TBI.

tion device. Furthermore, the excess catecholamine can lead to increased contractions or spasms of the small coronary vessels, which can subsequently cause myocardial ischemia and hypoxia [6-8]. In contrast, in cases with acute brain lesions, the body is in a state of stress, while the sympathetic-adrenal system is in an excited state, thus leading to an increased secretion of catecholamine, epinephrine, and neuropeptides. This increased secretion subsequently increases the autonomic dysfunction that is characterized by sympathetic nerve hyperactivity and parasympathetic nerve hypoactivity, which subsequently result in strengthened cardiovascular activity, spasm, coronary artery contraction, and ultimately induced ischemic heart damage [9, 10].

The findings of the current study revealed that myocardial ischemic injury occurred 6 h after the acute brain injury, and that significant changes occurred in the myocardial microcirculation and regional activities after 3 days. Therefore, patients with brain injury should receive comprehensive care, and close monitoring of their cardiac function should be performed. When brain disease is being treated, active treatments should be used to protect the myocardial function and prevent excessive dehydration or over-hydration, thereby ensuring that the patients survive the acute stage and maximizing their chances of recovery [11, 12].

RTMCE is a newly developed approach that involves the non-invasive monitoring of myocar-

Table 2. Comparison of the strain rates in each myocardial segment along the long axis of the left ventricle before and after injury

Detection time	S (s^{-1})	E (s^{-1})	A (s^{-1})
Pre-injury	1.98 ± 0.51	2.87 ± 0.60	2.22 ± 0.46
6 h after injury	1.88 ± 0.49	2.33 ± 0.58	1.96 ± 0.49
1 day after injury	0.87 ± 0.49*	1.08 ± 0.51*	1.02 ± 0.46*
3 days after injury	0.78 ± 0.49*	1.12 ± 0.41*	0.98 ± 0.56*

*Compared to results before and 3 h after the injury, $P < 0.05$. Data are presented as mean ± standard deviation.

dial microcirculation. It identifies blood perfusion at the myocardial microcirculation level in real time and facilitates quantitative analysis of the blood perfusion. In addition, previous research has demonstrated that A, β, and A·β can be used for quantitation of myocardial blood perfusion [13-15]. The findings of the current study demonstrated that the levels of A, β, and A·β in the different myocardial segments significantly decreased from 6 h to 3 days after the injury among the surviving dogs, compared to the pre-injury levels ($P < 0.05$). Therefore, this finding indicates that myocardial perfusion abnormalities can occur during the early stage of acute brain injury, and subsequently cause ischemic myocardial injury.

SRI is a new technique that is based on tissue Doppler technology, and is used to analyze regional myocardial activities. The SRI technique detects the regional myocardial activities throughout the cardiac cycle, and clarifies the small differences between the myocardial deformation of the different segments in various periods. In this context, the strain rate of the regional myocardium is less likely to be influenced by the overall movement of the heart or the dragging force from adjacent segments, thereby increasing its accuracy for quantitative analysis of the segment movements in the regional myocardium [7, 16, 17]. Injury to the longitudinal myocardial fibers of the subendocardium in the early stage of ischemia does not cause a change in the movement of the entire myocardium layer, although the shortened systolic and extended diastolic cycle lengths does affect the periodic change in the wall thickness. Therefore, SRI can identify ischemic myocardium at an earlier stage and provide a more reliable evaluation of the regional heart functions [18-20]. In the present study, both the brain function and the time had corresponding effects on the systolic and diastolic movement of the regional myocardium between 6 h and 3 days after the injury. Furthermore, the crests of the S, E, and A peaks decreased or disappeared, and the peak values decreased significantly, compared to the pre-injury values ($P < 0.05$). These findings indicate that regional myocardial dysfunction is caused by early stage myocardial ischemia.

The findings of the current study suggest that myocardial ischemic injury and regional functional changes can occur in the early stage of acute brain injury. The RTMCE and the SRI techniques provide real-time, noninvasive, and accurate measures of microcirculation perfusion in the impaired myocardium, as well as regional myocardial function, in patients with acute TBI. Therefore, we suggest that microcirculation perfusion is a new clinical indicator for the early and rapid diagnosis of brain-heart syndrome in acute TBI, and that it can facilitate timely clinical decision-making to protect myocardial function.

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Disclosure of conflict of interest

None.

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