Biomedical Research 2017; 28 (15): 6781-6785 *ISSN 0970-938X*
www.biomedres.info

Hemodynamic analysis of brain death patients using pulse-induced contour cardiac output (PiCCO).

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Abstract

The aim of this study is to investigate the hemodynamic characteristics of brain death patients *via* Pulse-Induced Contour Cardiac Output (PiCCO). 20 brain-death patients were included in the test group, and 20 with GCS ≥ 8 were included in the control group. The hemodynamic characteristics Pre-load (ITBVI/EVLWI), Cardiac Pump Function: (CI/SI/GEF/CFI/dPmax), Post-load: (SVRI) were collected by PiCCO at 0, 6, 12, 24 and 48 h were compared between 2 groups, dopamine and pituitary hormone can be used in some unstable patients in the test group. The preload ITBVI in test group at 0 h was lower than the control group (P<0.05), but no difference after volume management at 6 h. After volume management, the result of post-load SVRI in the test group decreased significantly compared with the control group (P<0.01); there were no significant differences of the results of HR, CI and SI between two group, but the results of GEF, CFI and dPmax decreased in the test group (P<0.01), which indicated the decrease of contractive force of cardic. Unstable hemodynamic was common in brain-death patients, with the decrease of the pre-load, post-load and contractive force of cardic.

Keywords: Brain death, Hemodynamic, Pulse-induced contour cardiac output (PiCCO), Organ transplantation.

Accepted on July 10, 2017

Introduction

According to the data released by the National Health and Family Planning Commission (NHFPC), People's Republic of China (PRC), each year about 300,000 patients are currently in urgent need of organ transplants, while the annual number of organ transplantation are only approximately 1 million, with a huge gap between organ supply and demand [1,2]. On Jan 1, 2015, the use of organs from executed prisoners was officially abolished nationwide [3]. Since then, the organs for transplantation have been entirely from voluntary contributions of citizens, and an organ donation from dead patients has become the main source of organs [4]. Although the organ donors that died from cardiac death have increased year by year, the organ supply from brain-dead donors is still the best source of the current field of transplantation, and the determination of brain death is more conducive to the smooth implementation of organ donation [5]. After the death of the brain, there are a series of pathophysiological changes, including hemodynamical, endocrine, metabolic and inflammatory reactions, etc., which can affect the long-term survival of the graft and recipient *via* the organ of the donor [6,7]. Of the pathophysiological changes in brain deaths, the most prominent manifestation is the hemodynamical instability [8]. A British study showed that by hemodynamical support and hormone replacement therapy, 84% of the donors whose initial assessment did not meet the standards of organ donation donor was finally able to donate organs [9].

After brain death, the hemodynamical changes are really complex [10]. Some studies suggested in the early stage of acute brain death, there could be the Cushing reflex, with sudden high blood pressure and slow heart rate, followed by a "sympathetic storm" of the sympathetic nervous excitement and massive release of catecholamine's, as well as rapid increase in cardiac output, mean arterial pressure, heart rate and oxygen delivery volume[11]; about 60 min later, there was the loss of sympathetic tone and significant reduction of peripheral vascular resistance, resulting in insufficient blood perfusion of vital organs and microcirculatory dysfunction. The "Sympathetic storm" after brain death can also lead to myocardial ischemia, myocardial injury and other cardiac structural changes, causing arrhythmias and decreased cardiac functions [12]. However, there have been rare clinical studies on the hemodynamics after brain death in human, in particular the reports on the comprehensive hemodynamical characteristics of brain-dead patients by pulse-indicated continuous cardiac output monitoring system, Pulse-Induced Contour Cardiac Output (PiCCO).

PiCCO, using the Transpulmonary Thermodilution Technique (TPTD) and the pulse contour analysis technique, can provide precise hemodynamical monitoring and clinical directions. With the thermodilution technique, Cardiac Output (CO) can be measured, meanwhile, the Intrathoracic Blood Volume (ITBV), Extravascular Lung Water (EVLW), Systemic Vascular Resistance (SVR), Global Ejection Fraction (GEF), Cardiac Function Index (CFI), left ventricular contractility

index (dPmax), and many other indicators. ITBV has been proved by many scholars to be a repeatable and sensitive indicator which can more accurately reflect cardiac preload than Pulmonary Artery Occlusion Pressure (PAOP), Right Ventricular End-Diastolic pressure (RVEDV) and Central Venous pressure (CVP) [13,14]. EVWI is the only unique bedside quantitative measurement of pulmonary edema index of PiCOO. SVR can reflect peripheral vascular resistance; while GEF, CFI can dPmax reflect cardiac pump functions. Therefore, the 3 main hemodynamical elements: preload, afterload and cardiac pump functions can be fully demonstrated by PiCCO. In this study, PiCCO was used for the systematic research and analysis of the hemodynamical characteristics of patients diagnosed with brain death, so as to find out the basic laws of hemodynamics in brain-dead patients and to provide clinical practices with more reasonable hemodynamical support, with better protection of the organ functions and higher successful rate of organ procurement.

Materials and Methods

Group and criteria

The brain-dead patients admitted to the Intensive Care Unit (ICU) department of the Third Hospital of Hebei Medical University from Jun 2014-2016 were selected as the test group, while the same number of patients with brain injuries and stable hemodynamical conditions (GCS>8) were selected as the control group, and the features of the two groups matched in age, gender and risk factors and other aspects. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hebei Medical University. The informed consent is signed by immediate family members.

Inclusion criteria of the experiment group: 1. Brain death caused by severe Traumatic Brain Injury (TBI), cerebral haemorrhage, aneurysms and other causes, determined by the brain death criteria released by the Ministry of Health in 2003 and confirmed by Electroencephalography (EEG) and Rheoencephalography (REG). 2. 18-55 y of age, no medical history of coronary heart disease, heart failure, atrial fibrillation, diabetes and hypertension, etc. 3. The associated injuries were under control, without active bleeding, no infection or infection under control.

Exclusion criteria: 1. After cardiopulmonary resuscitation, associated with myocardial infarction, pulmonary embolism and other conditions affecting hemodynamical assessment. 2. Serious infection, tension pneumothorax, severe abdominal distension, gastrointestinal bleeding and other cases of out of control.

A total of 20 cases were included in the test group (18 organ donors), including 12 males (10 cases of severe TBI caused by accident or trauma, and 2 cases of bleeding aneurysm) age=19-51, average age=37; and 8 females (7 cases of severe TBI, and 1 case of cerebral haemorrhage), age=18-49, and average age=35. The control group included 20 cases of TBI patients with stable hemodynamical conditions (mean of GCS 10.6 ± 2.3, median of GCS 11, APACHE II 10.2 ± 2.7), including 12 males (average age=38) and 8 females (average age=39).

PiCCO monitoring and data collection

After inclusion, the patients all received subclavian vein puncture or internal jugular vein puncture and femoral artery puncture to place the PiCCO duct, which was connected to multifunctional Philips monitor, and the hemodynamical monitoring was conducted by the thermodilution technique. At 0 h, 6 h, 12 h, 24 h and 48 h, the Temperature (T), the Heart Rate (HR), Arterial Blood Pressure (ABP), Cardiac Index (CI), the Stroke Index (SI), System Vascular Resistance Index (SVRI), Intrathoracic Blood Volume Index (ITBVI), Extra-Vascular Lung Water Index (EVLWI), Global Ejection Fraction (GEF), Cardiac Function Index (CFI), left ventricular contractility index dPmax and other data were recorded for all the patients, while the lactate, central venous oxygen saturation $ScvO_2$ were also monitored for tissue perfusion evaluation. The normal range of these parameters can be referenced in Table 1.

Table 1. *Reference range of all parameters.*

Parameter	Normal range	Unit
CI	3.0-5.0	L/min/m^2
EVLW	3.0-7.0	ml/kg
CFI	4.5-6.5	l/min
SVRI	1200-2000	dyn.sec.cm-5.m^2
SVI	40-60	ml/m^2
GEF	25-35	%
GEDI	680-800	ml/m^2
ITBI	850-1000	ml/m^2
ELWI	3.0-7.0	ml/kg

Quality control

For hemodynamically unstable patients with hypotension, intravenous infusion of dopamine was given to maintain a target systolic blood pressure at about 100 mmHg and mean arterial pressure at about 65 mmHg; for patients with diabetes insipidus, pituitrin was given to maintain the urine volume of 100-150 ml/h; the target level of HGB was maintained at 70 g/L or above; ice blankets and other measures were used to control the temperature at 36-37°C.

After inclusion, the volume status of the patients was evaluated, with ITBVI as target, and the ITBVI target level should be maintained at 850-1000 ml/m^2 (normal range) within 6 h by the methods of fluid infusion and diuretic.

Statistical analysis

SPSS19.0 statistical software was used for the analysis of the 0 h preload ITBVI with the t-test of two independent samples. Multi-level two-factor repeated measures analysis was used for the statistical analysis of the data of ABP, CI, SI, EVWI, SVRI, GEF, CFI, dPmax and so on at 6 h, 12 h, 24 h, and 48 h. P<0.05 was considered statistically significant.

Results

Preload ITBVI

After inclusion, the average ITBVI in the test group was 707.65 ± 103.62 ml/m^2, and it was 886.60 ± 87.30 ml/m^2 in the control group, with the difference of 78.95 ml/m^2. After the t-test of two independent samples, t=5.096, P<0.01, and the difference was statistically significant. The ITBVI l in the experimental group was significantly lower than it in the control group. For the test group, 1200 ± 293.5 ml solution was given at the first 6 h. After crystalloid fluid volume dopamine management after inclusion, the ITBVI was measured at 6 h, since the ITBVI was not comparable before hemodynamic interventions and the results of ITBVI in the test group and the control group were all within the normal range (850-1000 ml/m^2), with the average values of 882.40 ± 46.79 ml/m^2 and 906.55 ± 51.73 ml/m^2, respectively. After the t-test of the two groups, t=1.548, P=0.13, and the difference was not statistically significant. After volume management, the preload levels in the two groups were similar (Table 2).

Table 2. Analysis of pre-load ITBVI (ml/m^2).

	Experiment group	Control group	t	P
0 h	707.65 ± 103.62	886.60 ± 87.30	5.096	<0.01
6 h	882.40 ± 46.79	906.55 ± 51.73	1.548	0.13

System vascular resistance index SVRI and cardiac function

The body temperatures of the two groups were controlled at 36-37°C. Because of the hemodynamical instability in the patients of the test group, the patient also presented hypotension and sinus bradycardia, dopamine was pump to achieve target blood pressure, with the dosage of 5-10 μg/kg·min^{-1}. Also, 6 patients were given pituitrin for urine control. The P values of the time-dependent effects of the statistical indicators of the two groups were all >0.05, not statistically significant. With the premise that the patients of the test group were given dopamine and pituitrin, there were no significant differences of the results of HR, CI and SI between two groups; the result of SVRI in the test group decreased significantly compared with the control group (P<0.01), indicating statistical significance. Also, the results of GEF, CFI and dPmax decreased in the test group compared with the control group, and the differences were statistically significant (P<0.05). However, the EVWI level increased in the experimental group compared with the control group, but the differences was not statistically significant (P>0.05) (Tables 3 and 4).

Table 3. Cardiac post-load in brain-death patients compared with control group.

Groups		Brain-death	Control
MBP (mmHg)	6 h	102.9 ± 10.2	72.8 ± 8.3*
	12 h	101.4 ± 11.7	77.3 ± 7.6*
	24 h	109.5 ± 13.6	73.9 ± 6.9*
	48 h	97.7 ± 12.8	80.1 ± 5.7*
SVRI (dyn × s × cm^{-5} × m^2)	6 h	2148.23 ± 160.37	1416.15 ± 103.62*
	12 h	1921.18 ± 123.69	1340.16 ± 99.47*
	24 h	1963.87 ± 110.74	1315.22 ± 89.61*
	48 h	1842.61 ± 104.63	1457.95 ± 112.5*

Note: Compare with control group, brain-death group, *P<0.05.

Table 4. Heart function comparison between 2 groups.

Groups		Brain-death	Control
EVWI (ml/kg)	6 h	6.67 ± 0.56	5.64 ± 0.32
	12 h	6.0 ± 0.37	6.57 ± 0.53
	24 h	5.49 ± 0.69	6.29 ± 0.64
	48 h	5.63 ± 0.41	5.83 ± 0.39
GEF (%)	6 h	26.33 ± 2.16	31.08 ± 2.14*
	12 h	25.66 ± 1.98	31.12 ± 2.56*
	24 h	24.30 ± 2.07	32.71 ± 2.49*
	48 h	26.68 ± 2.06	31.8 ± 2.71*
CFI (L/min)	6 h	4.02 ± 0.36	4.76 ± 0.67*
	12 h	4.17 ± 0.49	5.12 ± 0.39*
	24 h	4.26 ± 0.52	5.38 ± 0.57*
	48 h	4.41 ± 0.61	4.90 ± 0.68*
dPmax (mmHg/s)	6 h	1296.36 ± 110.39	1600.46 ± 109.32*
	12 h	1294.49 ± 108.42	1765.32 ± 124.11*
	24 h	1320.87 ± 114.27	1786.9 ± 116.27*
	48 h	1364.21 ± 125.64	1800.28 ± 127.46*

Note: Compare with control group, brain-death group, *P<0.05.

Tissue perfusion index

The levels of lactic acid and $ScvO_2$ of the control group were both within the normal range, while 5 cases in the test group presented blood lactate level>2.0 mmol/l, and $ScvO_2$<70% in 3 patients. After fluid resuscitation and vasoactive medications, the lactate levels in all patients returned to normal levels within 12 h.

Discussion

The studies on hemodynamics after brain death are mostly animal experiments, and are mainly on the acute phase or early phase of brain death. Experimental animals often die after a few hours of brain death, without long-term survival. Also, as known from clinical practices, in the brain death in humans, a full range of comprehensive support and treatments in the ICU are also needed to maintain a short-term survival with the vital organ functions. This study, as an exploratory attempt on the hemodynamical characteristics of the human brain death, and initially proved that the significantly decreased systematic vascular resistance and the cardiac function are the major reasons of the hemodynamical disorders in the late phase or the non-acute phase of brain death, which is consistent with the conclusions of the animal studies. The decreased peripheral vascular resistance should be related with the sympathetic failure and the failure of catecholamines, which is easy to understand. However, for the decrease in cardiac function, animal studies have provided a variety of explanations. Catecholamine may release occurring with surgical stimulation during the organ procurement procedure and this technique increases viability of transplanted organs [15]. It also has been found that the degree of the sympathetic storm speed and increased intracranial pressure should be positively correlated, while the rapid increase in intracranial pressure often accompanied by rapid depletion of catecholamines and earlier circulatory failure [16]. The decrease in the cardiac function could be related to the reduced coronary blood flow caused by the dropping of the post-load after the brain death. For example, if the coronary blood flow was maintained after brain death in canines, there would not be cardiac dysfunction [17]. In this study, dopamine was used to maintain blood pressure. There was no obvious decrease of diastolic blood pressure, indicating the adequate perfusion of the heart itself, with sufficient preload to maintain normal cardiac ejection and tissue perfusion. But, the decreases in myocardial contractility index indicated other reasons of the cardiac dysfunction other than the coronary ischemia. It was also found in this that most brain-dead patients had volume depletion, or even hypo perfusion in vital organs, which might be related with the relative volume depletion caused by the vasodilatation caused by the decrease of vascular tone after brain death. The indicators of traditional CVP have been proved to have poor correlation with the preload. And the active PiCCO monitoring of these patients could be more precise and effective than the volume management by ITBVI and EVWI [18].

In this study, the data at 0 h, 6 h, 12 h, 24 h and 48 h were used to reflect time as an effective factor. Based on previous animal experiments, the hemodynamical fluctuations after acute brain death should be within the first few hours. However, after the determination of brain death in humans, the acute phase should be definitely passed, and the entire study was conducted in the late stage the platform stage of brain death. The medication of dopamine and other drugs could maintain the relatively hemodynamical stability in brain-dead patients. Statistical analysis also proved that the hemodynamical changes were irrelevant to the time factor within the first 48 h, or it can be said that there was no significant difference of the hemodynamical characteristics at various time points, which can save a lot of time cost and data processing for further studies.

Some studies in other countries have reported that after adequate fluid resuscitation, 80%-90% of patients require vasoactive drugs to maintain circulation [19]. So far, there have been no randomized controlled trials to compare the pros and cons of various vasoactive drugs. Norepinephrine may affect cardiac functions in the beginning after the heart transplantation; it would reduce the donor's vital organ blood supply [20]. Dopamine is still the first-line treatment, and it is still found that dopamine has other effects such as immunoregulation, anti-inflammation and lung protection, etc., [21-23]. Some foreign studies have shown that for the patients with brain death in whom dopamine cannot maintain hemodynamical stability, pituitrin can be used to increase systemic vascular resistance [24,25]. In this study, 3 cases of patients after brain death needed the administration of pituitrin. Even it was designed for urine control; it could significantly reduce the amount of dopamine, which is consistent with the results of studies abroad.

Due to the small sample size and the observation of hemodynamics only within 48 h after brain death, this study could only provide a preliminary investigation on the hemodynamical characteristics after brain death. Further studies and analyses should be carried out for the hemodynamical influences by the different types of TBI, different time lengths of brain death, the cardiac reserve status before brain death, clinical care such as body turning, the changes of the dopamine pumps, etc. This study could also provide some references for the hemodynamical support and organ protection of the donors, so as for increase of the organ supply and the development of organ transplantations.

Acknowledgements

This work was funded by Key Task of Medical Science in Hebei Province in 2016 (20160586).

Conflict of Interest

The authors declare that they have no conflict of interest.

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