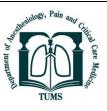


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# Cardiac Function in Brain Death, Usage of Advanced Hemodynamic Monitoring

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#### ABSTRACT

**Background:** This study used advanced hemodynamic monitoring along with simultaneous echocardiography to assess donated heart function of brain death patients using advanced hemodynamic monitoring and its efficacy in organ donation. **Methods:** Forty-eight brain death patients who were candidates of heart donation on the basis of primary standard investigations were selected with purposive and convenient sampling methods. They were investigated with advanced hemodynamic monitoring after echocardiography and primary assessments and the gleaned data were recorded.

**Results:** Echocardiography showed that LVS (left ventricle size) and LVF (left ventricle function) were normal in %100 and %87.5 of patients, respectively. LVEF (left ventricle ejection fraction) was <%50 in %12.5 and >%50 in %87.5 of patients. SVR was smaller than 1200 at the beginning of the study that reached %54.4 at the end of the study. CI (cardiac index) was < 2.4 in %16.7 of the patients at the onset of the study that reached %25 at the end. Reduction of CI and SVR in patients with EF <%50 was significantly higher than that in patients with EF>%50.

**Conclusion:** Given the extensive pathological changes in the cardiovascular system exerted by brain death, advanced hemodynamic monitoring, if performed continually, can greatly aid in managing inotropic drugs in these patients, decision-making for managing intravascular volume, creating hemodynamic stability, and finally, preventing deterioration of function of the donated heart and loss of a donated organ.

Giant strides taken in medicine have driven many disappointed heart failure patients to return to an optimistic life through heart transplant. The first organ transplant in the world was accomplished in 1935 followed by numerous achievements thereon. A revolutionary advancement in organ transplant was achieved by the first successful heart transplantation in human in 1967 [1]. Since then, many end-stage heart

patients have returned to normal life and heart transplant is rendered as the last line of treatment for these patients [2]. As a result, the number of heart transplant candidates has outrun the number of heart donors leading to an imbalance between demand and supply in organ transplant [3]. Data published by Association of Organ Procurement Organizations (AOPO) indicate that only %31 of 9080 hearts donated in 2015 has been transplanted [4]. If all the

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donated hearts were transplanted, the problem of shortage of transplanted organs could be overcome round the globe. Physicians in charge of donated organ allocation hesitate whether to accept or reject the heart donated by a fully anonymous donor. This is because the acceptance of such a donated heart raises the possibility of encountering a myriad of adverse outcomes of transplantation ending in the rejection of the transplanted organ [5-6]. One approach to cope the shortage of transplanted hearts is the provision of better strategies for diminishing the probability of graft rejection. Despite meticulous clinical assessments performed in selecting transplant heart, physicians frequently face transplanted heart rejection and acute or chronic heart failure after transplantation. Nonetheless, it is not clear what percentage of donated hearts characterized as inappropriate for graft has been, indeed, appropriate for this purpose or, on the contrary, what percentage of accepted hearts has been, in fact, inappropriate for transplantation [7-8]. Maintenance of the life of vital organs in brain death patients is of utmost importance. To protect these organs, acceptable hemodynamic conditions ought to be created and maintained for the patients. Hemodynamic instability is a common occurrence in brain death patients [9]. Moreover, the rate and degree of this hemodynamic instability is directly correlated with the time of incidence of brain death, and subsequently, with the degree of deterioration of autonomic nervous function [10]. Increased intracranial pressure and brain stem ischemia lead to cessation of vasomotor center resulting in reduced "blood pressure autoregulation", decreased sympathetic tone, extensive and severe reduction of systemic vascular resistance, and extensive vasodilation [11]. Consequently, intravascular volume decreases due to the formation of venous blood pools and hypotension, sometimes predisposing to multifactorial exacerbation of cardiac and organic functions [12-13]. Hence, the hemodynamic management of these patients is highly significant and includes routinely and conventionally a combination of electrolyte and inotropes replacement along with vasopressors so that a mean arterial pressure (MAP) of 70 mmHg is achieved for patients. The excessive use of norepinephrine and various vasopressors increases the possibility of destruction of graft function; also, the excessive use of fluids enhances pulmonary edema in these patients [14-15]. Conventionally, a reduced left ventricle ejection fraction in the donor is considered as an important predictor of acceptance or rejection of the transplant heart [16]. In previous guidelines, the cut-point of EF for initial acceptance or rejection of the donated heart was %45 whereas more recent studies have reported this rate to be %50 [17-19]. Nevertheless, some evidence suggests that, in some cases, the donated hearts that lacked the standards of a complete heart for donation or had a low EF demonstrated high efficiency after graft [5]. Although

heart transplant centers avoid transplantation of hearts with EF<%50, some studies revealed that the annual outcome of patients receiving marginal donor was the same as that of patients that received hearts with normal EF indicating that EF is repairable provided the heart is located in a normal environment [20]. Lack of proportion between the number of heart failure patients and donated hearts has brought about much debate concerning the use of the hearts donated by marginal donors [17,21]. Besides the assessments and wide challenges involved in EF of donated hearts, the investigation and maintaining the circulatory system of a brain death patient is highly challenging, and hemodynamic assessments without the use of advanced hemodynamic monitoring is a stubborn, if not impossible, task [22]. Today, the application of various hemodynamic monitoring methods is increasing progressively. The use of these methods in procuring the donated organs will help greatly to maintain the donated organ and enhance patient care and assessment before and after graft [21, 23]. Whenever the brain death of a victim is definitely diagnosed and the heart is donated, echocardiography is performed for the patient to assess the status of functioning of the ventricles and valves. However, the final decision for accepting or rejecting the donated heart for transplanting to the receiver is made by the heart surgeon after carefully observing and evaluating the heart function and hemodynamic stability [24]. The present showed researchers' experience that although echocardiography provided accurate information on the donated heart, in some cases it was rendered as inappropriate for graft after the surgeon observed the heart closely, though it was approved for graft by echocardiography findings and thus, no heart transplant was carried out [25]. Additionally, considering that cardiac arrest and hemodynamic instability are the main causes of lack of heart donation, the following points should be observed to maintain the donated organs that qualify for donation along with consent of the donor's family: management of the hemodynamic conditions of the patients with strict guidelines and advanced hemodynamic monitoring instruments, real-time investigation of the patients, and provision of healthcare strategies on this basis [26]. Most studies conducted on hemodynamic changes in brain death cases have centered on in vitro and animal studies so that very few studies have dealt with hemodynamic changes in brain death patients [27]. Consequently, the present study used advanced hemodynamic monitoring along with simultaneous echocardiography to assess donated hearts and provide better information on heart status. In this way, better judgments could be made on heart donation and transplantation. The second goal of the study was the real time assessment of brain death patients using advanced hemodynamic monitoring and its efficacy in organ donation.

## Methods

This cross-sectional analytic study was conducted on a population of brain death candidates of organ donation at Masih Daneshvari Hospital in Tehran, Iran during 2016-2018. They were selected with purposive convenient sampling method. The researchers, in coordination with Organ Processing Unit of Masih Daneshvari Hospital, selected 48 brain death candidates of heart donation on the basis of primary assessments and conventional standards. They underwent echocardiography and were then investigated with advanced hemodynamic monitoring. The inclusion criteria were: age less than 45 years, no previous history of heart disease, lack of affliction with hepatitis B, hepatitis C, and HIV, no history of smoking or drug addiction, no history of malignancy or cancers, and acceptable cardiac function approved by echocardiography. Data were collected with a researcher-made questionnaire consisting of three parts. The first part included demographics like age, gender, height, weight, cause of brain death, history of taking medicines, history of cardiac risk factors, history of acute and chronic non-cardiovascular disorders, history of other acute/chronic disorders, etc. The second part of the tool consisted of paraclinical and clinical information such as echocardiography findings including left ventricular size (LVS), left ventricular function (LVF), right ventricular size (RVS), right ventricular function (RVF), ejection fraction (EF), pulmonary artery pressure (PAP), tricuspid valve (TV) status, left ventricular muscle volume (LVMV), mechanical ventilation settings, history of cardiac arrest and CPR, administration of inotropic drugs, taking of other drugs, and conventional hemodynamic monitoring including pulse oximetry, mean arterial pressure, central vein pressure, ECG, invasive blood pressure, blood pressure, heart rate, and temperature. Generally, an arterial line is inserted for all heart donation candidates to control blood pressure and a central venous line is inserted to control fluid volume status. These variables were monitored in a real time manner. The section on demographics was completed using patients' recorded files and the section on clinical and paraclinical information was completed by the researcher under supervision of hospital cardiologists and anesthesiologists. The validity and reliability of clinical and paraclinical tests have been assessed and approved by many studies and echocardiography findings are known as gold standard for assessing brain death candidates of heart donation. Simultaneously, suitable candidates of heart donation on the basis of echocardiography findings were plugged to Vigileo Monitor (MHM1E-Edwards Life sciences, Irvine, US) and underwent advanced hemodynamic monitoring. The variables "stroke volume (SV), stroke volume index (SVI), mean arterial pressure (MAP), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), stroke volume variation (SVV), cardiac index (CI), and cardiac output (CO) were measured and recorded. Then, using one-hour intervals, these variables were measured again and recorded. Given the brain death patients' short hospital stay, the researchers investigated all of the patients once simultaneously with echocardiography, and then in onehour intervals for two full hours. All the donated hearts in this study were finally transplanted to the patients. The gleaned data were analyzed with SPSS22 using repeated measures ANOVA, Friedman, and Pearson correlation coefficient.

## Results

The findings showed that the mean age of the study units was 28.61±9.07 years, the youngest was 15 and the oldest was 43 years old. Most patients (%86.4) were male with normal BMI (%68.2). The mean height of the patients was 167±5 cm, the mean weight was 61±14 kg, and length of brain death approval was 3±1 days. Mean systolic pressure (SBP) was 116.81±20.93 mmHg, mean diastolic blood pressure (DBP), 70.36±14.30 mmHg, mean arterial pressure (MAP), 82.81±18.91 mmHg, heart rate (HR), 94.5±12 bpm, temperature (T), 34.05±5.03° C, central vein pressure (CVP), 8.05±2.3 mmHg, and arterial oxygen saturation, 96.91±2.91. The cause of brain death of the patients was cerebrovascular aneurysm in %29, head trauma and impact in %50, and intracerebral hemorrhage (ICH) in %21. History of smoking and drug abuse was negative in %83 of patients. Given the suitable MAP in %25 of the patients, no inotropics were administered. Considering the hemodynamic condition, in %8 of the patients, dopamine and in %66 norepinephrine was used to control blood pressure and heart rhythm. The echocardiography findings are presented in (Table 1).

Left Ventricular Size (LVS), Left Ventricular Function (LVF), Right Ventricular Size (RVS), Right Ventricular Function (RVF), Ejection Fraction (EF), Pulmonary Artery Pressure (PAP), Tricuspid Valve (TV), Left Ventricular Muscle Volume (LVMV)

In echocardiography, the LVS was normal in all (%100) of the patients. LVF was normal in %87.5 of patients and %6 showed a mild disturbance. LVEF was <%50 in %12.5 of patients and >%50 in %87.5 of patients. RVS was normal in %95.8 and RVF was normal in %87.5 of patients. PAP was normal only in %79.2. Also, tricuspid valve status was normal in %84.2 of patients. The results of advanced hemodynamic monitoring are displayed in (Table 2).

Stroke Volume (SV), Cardiac Output Index (SVI), Mean Arterial Pressure (MAP), Systemic Vascular Resistance (SVR), Systemic Vascular Resistance Index (SVRI), Stroke Volume Variation (SVV), Cardiac Index (CI), Cardiac Output (CO)

The findings demonstrated that %50 of the patients had SVR<1200 at the onset of the study which reached %54.4 at the end of the study whereas in %66 of the patients, norepinephrine was used to control vascular pressure and tone (Figure 1).

Reduction of vascular resistance was significantly greater in patients with EF<%50 compared to those with EF>%50. Besides, CI was <2.4 in %16.7 of the patients at the beginning of the study that reached %25 at the end (Table 3).

Reduction of CI was significantly greater in patients with EF<%50 compared to those with EF greater than %50 (Figure 2).

**Table 1- Echocardiographic findings** 

Range	Frequency	Percentage	
	requeitcy	Tereentage	
Normal	48	100	
Abnormal	0	0	
Normal	42	87.5	
Abnormal	6	12.5	
≤50	6	12.5	
≥50	42	87.5	
Normal	46	95.8	
Abnormal	2	2.4	
Normal	42	87.5	
Abnormal	6	12.5	
≤20	38	79.2	
≥20	10	20.8	
Normal	36	75	
Abnormal	12	25	
	NormalAbnormalAbnormal $\leq 50$ $\geq 50$ NormalAbnormalAbnormalAbnormalState $\leq 20$ $\geq 20$ Normal	Normal48Abnormal0Normal42Abnormal6 $\leq 50$ 6 $\geq 50$ 42Normal46Abnormal2Normal42Abnormal6 $\leq 20$ 38 $\geq 20$ 10Normal36	

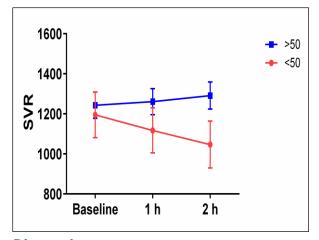
Time Variable	First measurement simultaneous with echo		Second measurement 1 h after echo		Third measurement 2 h after echo	
	Mean	SD	Mean	SD	Mean	SD
SV	63.8	18.1	65.7	25.3	59.6	14.2
SVI	38.5	8.3	39.9	13.1	34.1	8.1
MAP	82.9	18.7	80.1	15.8	81.5	13.0
SVR	1232.4	383.0	1229.5	387.2	1237.9	411.4
SVRI	1974.1	479.8	1903.8	653.1	2191.4	963.8
SVV	11.7	4.5	9.9	3.5	10.6	3.0
СО	6.0	1.7	5.9	2.1	5.6	1.1
CI	3.2	0.9	3.1	1.0	2.9	0.51

Table 2- Findings of advanced hemodynamic monitoring

Table 3- CI, SVR and SV changes in patients with EF≤%50 and EF≥%50

	Group	Group EF≤%50		EF≥%50		T-test	
Variable		Mean	SD	Mean	SD	1-test	
CI	Baseline	2.1	0.2	3.3	0.8	P=0.000	
	1h	2.1	0.1	3.3	1.0	P=0.000	
	2h	2.1	0.2	3.1	0.4	P=0.000	
SVR	Baseline	1600	121	1197	382	P=0.000	
	1h	1498	211	1203	391	P=0.000	
	2h	1423	147	1220	421	P=0.003	
SV	Baseline	44.6	3.6	66.5	17.7	P=0.000	
	1h	37.1	1.5	69.8	24.1	P=0.000	
	2h	43.1	1.5	62.1	13.3	P=0.000	

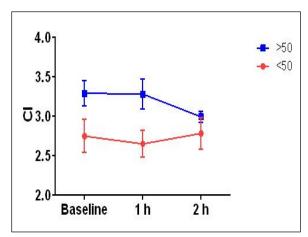
Figure 1- SVR changes in patients with EF≤%50 and EF≥%50



## Discussion

Studies on advanced hemodynamic monitoring after brain death have mostly focused on animal cases and have often been conducted in the acute or premature phase of brain death, i.e., immediately after induction of brain death in animals. Hence, an important difference between human and animal hemodynamic monitoring studies after brain death lies in the time of brain death investigation, since these studies are carried out on animals soon after induction of brain death whereas they are done on humans after some time lapse and approval of brain death. Another difference between animal and human studies pertains to patient hospitalization in the ICU/CCU and the wide range of therapeutic and pharmaceutical care given to maintain their lives. Thus, human hemodynamic monitoring would be impossible without considering the pharmaceutical, therapeutic, and care-giving variables [27]. Cushing reflex is created in the primary acute phase of brain death following increased intracranial pressure predisposing to sudden increase in blood pressure and reduced heartbeat. Sympathetic storm occurs after increased time of brain death due to overstimulation of sympathetic nerve and the sudden and severe increase in Catecholamine's level resulting in increased cardiac output, increased mean of MAP, heartbeat, and oxygen exchange. After the passage of 60 min following brain death, blood supply to other organs is impaired due to reduced sympathetic tone and severely decreased vascular resistance (VR) leading to microcirculatory dysfunction [25]. The results of the present study indicated that the mean SBP, DBP, MAP, HR, central vein pressure, and arterial oxygen saturation were normal in all patients. Given that death brain is medically approved after several days and considering that obtaining consent from the patient's family takes some time, thus, the present researchers faced brain death patients that were influenced by drugs and advanced care for maintaining hemodynamic stability. Therefore, there

Figure 2- CI changes in patients with EF≤%50 and EF≥%50



were differences in the vital signs of these patients compared to what is put forward by physiological discussions. So, it could not be alleged whether the patients under study that have been in the early stages of brain death have been afflicted with Cushing reflex or sympathetic storm or not. The study by Guo has referred to this limitation in human studies [27]. Reduction in SVR and CI in our patients approves that reduction in SVR and CI continues in brain death patients even after administering vasopressors and inotropes, finally resulting in cardiac dysfunction. The findings of most studies suggest that SVR and cardiac function (CF) are diminished significantly after brain death serving as the main causes of hemodynamic instability and finally, cardiac arrest in the end stages of brain death, a finding that is consistent with the results of animal studies [25]. The study by Szabo et al. demonstrated that induction of brain death in animals leads to %40 reduction in SVR in the first hour. Yet, as the intravascular fluid volume is replaced, the pumping function of the heart is maintained. Reduced sympathetic tone together with vascular dilation predisposes to variations in heart filling volume that characteristically justifies the hemodynamic changes and instability in brain death patients [28]. Vascular dilation and reduced afterload lead to decreased blood supply to coronary vessels and reduced blood circulation in vessels, ultimately resulting in diminished cardiac preload. Research shows that if the reduced intravascular volume and diminished blood supply to coronary vessels are corrected, the brain death patient will not suffer from cardiac dysfunction [26]. Considering the availability of global guidelines for selecting donated hearts for transplant, most echocardiographic parameters of the patients were similar to those of other studies. In previous guidelines, the cut-off point for EF for initial acceptance or rejection of the donated heart was %45 and 40% [17-18] whereas more recent studies have reported this rate to be %50 [19]. Given the low number of donated hearts and

considering disparities in the studies in this field, our study selected patients with EF 2%45 as heart transplant candidates. Patients with EF>%45 are instantly rendered as heart donation candidates; yet, patients with EF<%45 are obliged to first stabilize their condition via administering hormones (insulin, methyl prednisolone, vasopressin, and thyroid hormone); then, a pulmonary artery catheter is inserted in place to fully investigate their hemodynamic condition. In the case that CI is greater than 2.4, MAP is greater than 60 mmHg, CVP is 4-12, SVR is 800-1200, and the rate of inotropes dopamine and Dobutamine is less than 10 micrograms in terms of weight, the heart is assessed again and selected as donation candidate again [18]. In the present study, 6 patients with EF<%50 were rendered as heart donor candidates after objective visual examination by a cardiologist. The results of this study found a significant positive correlation between "CI of the donated hearts" and "LVEF and LV Function. Although this correlation is not statistically high, it demonstrates that these two parameters are unidirectional. Moreover, there was a direct significant correlation between RV Function and Cardiac Index (CI). Also, there was a direct weakly significant correlation between RV Size and Cardiac Index (CI). The most important criteria for selecting the transplant heart on the basis of the guideline mentioned in "Introduction" were LVEF>%45 and CI>2.4. These two parameters were directly and significantly correlated in this study; however, the most important cause of low correlation between the two was the presence of three outlier samples that were distinct from other samples. These three samples had LVEF>%45 and CI<2.4 justifying the reduced correlation. Considering that the echo parameters are individual-dependent and the individual's experience contributes to its measurement while CI parameter is completely measured by a device, it may be concluded that to ensure of the definite functioning of the donated heart, it should be assessed by the two methods since if we apply only echocardiography, considering the donated hearts, it is probable that the donated heart may not have an acceptable function leading to rejection of the donated heart or post-graft complications. The results of a integrative review also revealed that monitoring and hemodynamic support of brain death patients that qualified for organ donation led to improved organ performance and finally to organ donation. This will help to overcome the shortage of donated organs [28]. The results of this study were consistent with those of other studies. This highlights the importance of simultaneous use of both echocardiography and hemodynamic monitoring to make appropriate decisions for accepting or rejecting donated hearts. The study by Serban et al. also emphasized the concurrent use of hemodynamic monitoring and echocardiography in investigating the donated hearts and recommended the use of these equipment for identifying and assessing the donated hearts in a better way.

## Conclusion

Given the wide-spectrum pathological changes created in the cardiovascular system by brain death, advanced hemodynamic monitoring performed continually can aid greatly in managing inotropic medicines in brain death patients, making decisions for managing intravascular volume, and finally, creating hemodynamic stability, preventing deterioration of the donated heart, and loss of a donated organ.

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