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■증 례■

Successful Heart Transplantation after Dobutamine, Glucose-insulin-potassium, and Hormone Therapy in a Hemodynamically Unstable Cadaveric Heart Donor

− A Case Report −

So Yeon Kim, M.D., **Shin Ok Koh,** M.D., **Young Chul Yoo,** M.D., **Ha Kyoung Kim,** M.D., **Tae-Jin Yun,** M.D.*, **Eun-Ji Chang,** M.D.* and **Sungwon Na,** M.D.

Department of Anaesthesiology and Pain Medicine, Anaesthesia and Pain Research Institute, Yonsei University College of Medicine, *Division of Pediatric Cardiac Surgery, Asan Midical Center, University of Ulsan College of Medicine, Seoul, Korea

The major limitation to heart transplantation is the shortage of donor organs. In order to increase the cardiac donor pool, it is important to maintain stable hemodynamics and closely monitor cardiac function in cadaveric organ donors or potent donors. Recently, management of a potential cardiac donor pool has focused on aggressive hemodynamic management protocols and dobutamine stress echocardiography. In our case, management with low dose dobutamine, glucose-insulin-potassium (GIK), and hormone therapy reversed heart failure following brain death and the heart was successfully transplanted. We suggest that aggressive hemodynamic management with low-dose dobutamine, GIK, and hormone therapy can result in the recruitment of more cadaveric hearts in marginal conditions.

Key Words: brain death, cardiomyopathy, echocardiography.

The shortage of donor hearts for cardiac transplantation is exacerbated by the exclusion of those that exhibit reversible myocardial dysfunction induced by brain death.[1-4] Clinical and laboratory data have described acute myocardial dysfunction after brain injury, which prevents heart donations from cadaveric organ donors. Recent report recommend hemodynamic and metabolic management should be performed before the organ is declined when donor left ventricular dysfunction is present.[5,6] We report a case of a successfully transplanted heart after the reversal of heart failure following brain death, which was reversed using low dose dobutamine, GIK, and hormone.

CASE REPORT

A 39-year-old previously healthy man presented to an emergency department (ED) with loss of consciousness following a seizure. His medical history, obtained from his family, was unremarkable. There was no past history of trauma or neurologic disease. Computed tomography revealed paraventricular hemorrhage from an arteriovenous malformation. An emergency hematoma drainage was performed, but brain stem death was suspected. The patient was transferred to our university hospital for organ donation. The patient was immediately admitted to the intensive care unit (ICU) via the ED.

On arrival at the ICU, the patient presented with a blood pressure of 146/106 mmHg, heart rate of 125 bpm, and rectal temperature of 34.6°C. He was in a coma, with a Glasgow Coma Scale score of 3 with fixed, nonreactive pupils 5 mm in diameter bilaterally. Because he was not hypotensive, infusions of dopamine, epinephrine and dobutamine, which had been started at the previous hospital, were stopped. The concentration of each drug was not well documented. Soon after, the patient became hypotensive, so we started a norepinephrine infusion of 0.3 μg/kg/min and vasopressin of 0.03 units/min. The dose of norepinephrine was reduced to 0.1 μg/kg/min within 2 hr after admission. A pulmonary artery catheter (PAC, Swan-Ganz CCOmbo CCO/SvO_2™, Edwards Lifesciences LLC, Ir-

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Correspondence to: Sungwon Na, Department of Anaesthesiology and Pain Medicine, Anaesthesia and Pain Research Institute, Yonsei University College of Medicine, 250, Seongsanno, Seodaemun-gu, Seoul 120-752, Korea
Tel: 82-2-2228-6456, Fax: 82-2-312-7185
E-mail: nswksj@yuhs.ac

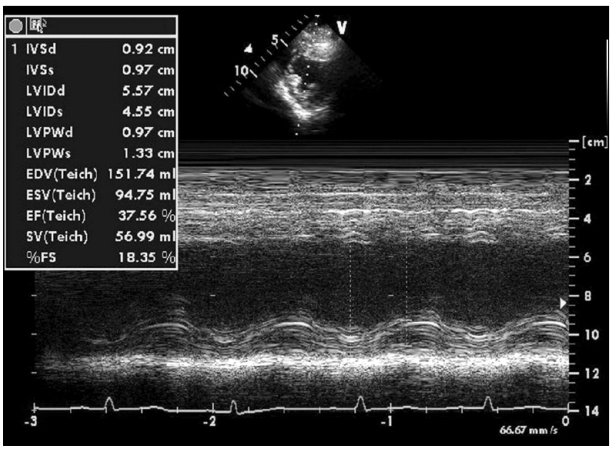

Fig. 1. M-mode transthoracic echocardiography in parasternal short axis view two hours after ICU admission. From this view, left ventricle end-diastolic diameter/end-systolic diameter = 56/46 mm and ejection fraction 33% were measured.

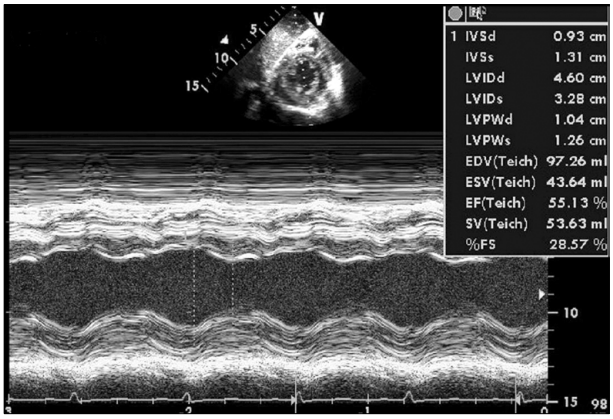

Fig. 2. M-mode transthoracic echocardiography in parasternal short axis view 12 hours after ICU admission. From this view, left ventricle end-diastolic diameter/end-systolic diameter = 48/34 mm and ejection fraction 59% were measured.

vine, CA, USA) was inserted via the right jugular vein and connected to an analysis system (Vigilance™, Edwards Lifesciences LLC, Irvine, CA, USA). The patient's cardiac index was 3.5 L/min/m^2 with mixed venous oxygen saturation of 79%. An initial electrocardiogram upon arrival at the ICU showed normal sinus rhythm at 85 bpm. Chest X-ray, chemistry, complete blood count, and urinalysis did not show any particular abnormalities.

Two hours after ICU admission, the patient presented with a blood pressure of 117/81 mmHg, heart rate of 82 bpm, central venous pressure of 9 mmHg, cardiac index of 3.4 L/min/m^2, and rectal temperature of 35.1°C. Transthoracic echocardiography revealed a slightly enlarged left ventricle (end-diastolic diameter (EDD)/end-systolic diameter (ESD) = 56/46 mm) and severe global hypokinesia of the left ventricle (Fig. 1). The left ventricular ejection fraction (LVEF) was measured at 33% by m-mode. Diastolic function could not be measured due to summation of mitral inflow waves from tachycardia. Valvular abnormalities were not observed except trivial mitral and tricuspid regurgitation. Right ventricular systolic pressure measured from maximal tricuspid regurgitation jet velocity was within normal limits. Stress-induced cardiomyopathy was presumed considering the patient's medical history, lack of myocardial ischemia evidence by electrocardiogram, and normal cardiac enzymes. We started dobutamine at 2 μg/kg/min and a mixture of insulin, glucose and potassium (regular insulin 325 unit + potassium chloride 80 mEq in 50% dextrose water 500 ml) at 10 ml/hr. Intravenous methylprednisolone sodium succinate (Solu-medrol, Pfizer Pharm., Seoul, Korea) 250 mg and levothyroxine sodium (Synthyroid, Bukwang Pharm., Seoul, Korea) 50 μg was administered by nasogastric tube despite the fact that the results of thyroid function tests were not available at that time. Two serial clinical testing sets for brain reflexes were performed, including an apnea test, which showed absence of all cranial nerve function. The electroencephalogram demonstrated extremely low amplitude background activity without any physiological variability or regional activities, compatible with brain death. Vital signs were maintained stable and cardiac index was measured from 3.4−5.3 L/min/m^2. Mixed venous oxygen saturation ranged from 79−91%.

Twelve hours after ICU admission, the patient presented with a blood pressure of 136/94 mmHg, heart rate of 97 bpm, central venous pressure of 3 mmHg, cardiac index of 3.9 L/min/m^2, and rectal temperature of 35.9°C. Compared to the previous echocardiography results, left ventricular size was decreased to EDD/ESD = 46/33 mm and the previously observed severe hypokinesia of the left ventricle was no longer seen (Fig. 2). LVEF was improved to 59%. Diastolic function was still unmeasureable. Pulsed wave Doppler measured at the left ventricular outflow tract, which reflects stroke volume, was improved from 9.6 cm to 12.2 cm. The family, intensivists and surgeons agreed to donate the patient's heart.

The donated heart was transported to another university hospital to be transplanted into a patient with dilated cardiomyopathy. Echocardiography performed 20 days after the transplantation showed normal left ventricular systolic function (EDD/ESD = 48/34 mm, LVEF = 62%). There was no regional wall motion abnormality and mitral inflow showed normal pattern (E = 98 cm/s, A = 31 cm/s, E/E' = 14). Grade I mitral and tricus-

pid regurgitation was noted. Myocardial biopsy demonstrated no evidence of rejection and coronary angiogram was normal.

DISCUSSION

Despite marked improvements in medical or surgical interventions, heart transplantation often has been the only available and curative treatment modality for end stage heart failure patients. However, the major limitation of heart transplantation is donor heart shortage. Two approaches can be considered for settling this shortage issue. One is to adopt aggressive management for cadaveric donors to increase the quantity of available organs, and the other is to recruit marginal hearts such as those from aged donors, with minimal coronary artery disease, requiring high doses of inotropes or showing acute systolic dysfunction induced by stress.[5,6)]

Cardiovascular instability is very common in brain death.[7)] Hypotension is more common in hypovolemic donors treated with vasopressors and in patients with diabetes insipidus who do not receive antidiuretic hormone.[8)] The goals of management of the hemodynamic status of the donor are to achieve normovolemia, maintain blood pressure, and optimize cardiac output so as to achieve gradients of perfusion pressure and blood flow that promote organ function with the use of the least amount of vasoactive-drug support.[5)]

Brain injury can induce myocardial dysfunction, which is evidenced by many clinical and experimental reports.[1-4)] This change is known to be caused by two mechanisms: microvascular spasm of coronary arteries induced by sympathetic activation, and direct cardiotoxicity of catecholamines.[9)] This derangement of cardiac function in brain injury is reversible, but the proportion of stunned myocardium is important for transplant success. Stress tests can play a role in identifying the amount of hibernated myocardium. In a prospective study, seven brain dead patients whose fractional shortening was under 30% underwent dobutamine stress echocardiography and three of them demonstrated improvement of wall motion abnormalities, whereas four of them did not.[10)] Those with reversible stress test results had normal troponin levels and gradual improvement by seven days after brain death; their clinical courses were similar to that of our patient.

It is reasonable for us to consider that increased intracranial pressure along with high doses of vasopressors administered in the primary hospital contributed to the development of stress-induced cardiomyopathy in this patient. On arrival at our ICU, he was on high doses of dopamine, dobutamine, and epinephrine. Several studies recommend low dose vasopressin as the first line vasoactive drug for brain death patients.[11-13)] We performed echocardiography evaluation only two hours after stopping the high-dose vasoactive drugs. Therefore, we reasonably doubt that the remaining effects of vasopressor overdose may have been the cause of stress-induced cardiomyopathy.

Appropriate management of cadaveric organ donors can recruit organs in marginal ranges. Two retrospective studies reported that thyroid hormone replacement in hemodynamically unstable patients can increase the number of available organs.[14,15)] Another study suggested that aggressive management of brain dead patients with fluids, steroids, insulin and levothyroxine may improve the quality and quantity of organs available for transplantation by decreasing vasopressor requirements and preventing cardiovascular collapse.[16)] The Canadian Critical Care Society recommended combined hormone therapy (thyroid hormone, vasopressin, and methylprednisolone) for hemodynamically unstable patients or those with reduced EF under 40% demonstrated by 2D echocardiography.[13)] Hormone replacement also improved one month post graft survival in heart transplant patients.[17)]

Another pharmacologic intervention for acute heart failure in brain dead patients is glucose-insulin-potassium mixture, or GIK solution.[18)] Dobutamine can disrupt the myocardial oxygen demand-supply balance by inducing tachycardia and hypotension which may aggravate myocardial ischemia. However, GIK is known to be as efficient as dobutamine in improving heart function in cadaveric donors without causing tachycardia or hypotension, although only one heart has been actually donated.[18)]

Two management protocols recommend combined hormone therapy (thyroid hormone, methylprednisolone, vasopressin, insulin) in heart donors with LVEF $<45\%$.[5,6)] In our patient, initial LVEF was measured at 33%. After combined hormone therapy, LVEF was improved to 59%. Using a combined approach of hemodynamic and metabolic management could result in a expansion of donor pool.

In conclusion, we report a case of heart function restored by combining aggressive hemodynamic management with low dose dobutamine, GIK, and hormone. Further study is needed to determine the outcome of donated hearts which show reversible heart dysfunction.

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