Acutely Severe Myocarditis Successfully Treated by Percutaneous Cardiopulmonary Support Applied by a Newly Developed Heparin-Binding Oxygenator and Circuits

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The feasibility of using the heparin-bound percutaneous cardiopulmonary support system (PCPS) for prolonged extracorporeal circulation in patients with acute severe myocarditis is demonstrated. The case histories of 2 patients with cardiogenic shock caused by acute myocarditis are presented; both were successfully treated with long-term PCPS using a newly developed heparin-binding oxygenator and circuits without changing the oxygenator. The courses of both patients remain uneventful more than 12 months after discharge. We also discuss the clinical aspects of using heparin-bound PCPS in patients with acute severe myocarditis.

(Ipn Circ J 1997; 61: 1037—1042)

Key Words: Cardiopulmonary bypass; Heparin; Myocarditis

Patients with acute idiopathic myocarditis present a variety of clinical manifestations. Although in the majority of patients with acute myocarditis the disease is self-limiting, the prognosis is poor in those who have life-threatening arrhythmia and/or progressive heart failure acutely deteriorating to shock. Aggressive interventions, including mechanical ventricular assistance, are keystones in the treatment of these high-risk patients, as spontaneous improvement may occur despite profound hemodynamic dysfunction. We present the cases of 2 patients with cardiogenic shock caused by acute severe myocarditis who were successfully treated long term with a percutaneous cardiopulmonary support system (PCPS) using a newly developed heparin-binding oxygenator and circuits with no change of the oxygenator.

Case Reports

Case 1
A 34-year-old Japanese woman was admitted to Omiya Medical Center because of fever, chest pain, and shortness of breath. The patient had been in good health all her life. She had a regular menstrual cycle and no coronary risk factors. Two days before entry she had noted systemic arthralgia and a fever of up to 38°C. Over the next 2 days, her symptoms progressed and pleuritic chest pain developed. She consulted her physician, who found ST elevation at leads V1–4 on the electrocardiogram (ECG). She was then immediately referred to the coronary care unit of our institute.

Physical examination on admission revealed the following. Her temperature was 37.5°C, heart rate regular and 79 beats/min, respiratory rate 28/min, systolic blood pressure 76 mm Hg, height 152 cm, and weight 49 kg. The third heart sound was audible, however, with no crackle in the lungs. ECG showed sinus rhythm, left-axis deviation, incomplete right bundle branch block, ST elevation on leads V1–4, and slight ST depression on leads I, II, aVL, and V5–6 (Fig 1A). The chest radiograph revealed slight
Fig 1. Electrocardiogram of case 1 on admission (A), on day 3 (B), on day 5 (C), and on day 70 (D).

Fig 2. Chest radiograph of case 1 on admission (left), on day 4 (middle), and on day 70 (right).

Fig 3. Time course of global right and left ventricular performance in case 1. Echocardiographic right ventricular (RV) areas at the papillary muscle level in the parasternal short-axis view were traced at end-diastole (EDA) and end-systole (ESA). RV fraction area changes (FACs) were calculated as \( \text{FAC}=[(\text{EDA} - \text{ESA})/\text{EDA}] \times 100\% \). IABP, intra-aortic balloon pumping; LVEF, left ventricular ejection fraction; PCPS, percutaneous cardiopulmonary support.
cardiomegaly and no lung congestion (Fig 2, left). The white blood cell count in peripheral blood was 3460/\,mm^3, the creatinine kinase (CK) level was 397 IU/L (160>) with a myocardial band of 20 IU/L, aspartate aminotransferase was 82 IU/L (5-40), and C-reactive protein was 2.0 mg/dl (0.25>). A 2-dimensional echocardiogram revealed no pericardial effusion, normal valves, slightly dilated right ventricle, normal left ventricular chamber size but severe right and moderate left ventricular global hypokinesis (Fig 3). Right-sided heart catheterization showed a right atrial pressure of 7 mm Hg, pulmonary arterial pressure of 18/13 mm Hg, pulmonary capillary wedge pressure of 13 mm Hg, and cardiac index of 1.5 L/min per m^2. Continuous administration of dobutamine and dopamine and intra-aortic balloon pumping (IABP) via the left femoral artery were initiated. However, following continued ORS prolongation, repetitive ventricular tachycardia was frequently observed on the ECG monitor. The patient's hemodynamic status continued to deteriorate, and systolic blood pressure decreased to 60 mm Hg 3 h after admission. Cannulas (16-Fr and 20-Fr) were inserted from the right femoral artery and vein, respectively, for PCPS. After insertion, the position of the venous catheter tip was immediately checked by echocardiography. PCPS was initiated at a rate of 3.0 L/min, with the patient's prompt return to hemodynamic stability. PCPS [Capiox SX custom pack (HP); Terumo, Tokyo, Japan] consisted of a hollow fiber membrane oxygenator without a heat exchanger, a centrifugal pump, polyvinyl chloride extracorporeal circuits, and polycarbonate connectors. To prevent blood coagulation, heparin was given continuously to ensure an activated clotting time of 150 sec, in addition to continuous infusion of nafamostat mesilate (0.02-0.05 mg/kg per hr).

On day 2, the plasma CK level gradually increased to 826 IU/L with a myocardial band of 26 IU/L. The patient had ventricular fibrillation, which was returned to sinus rhythm by cardioversion of 200 J. Immediately after the cardioversion, respirator care was started. We repeated the measurement of oxygen saturation of central venous blood, echocardiography, and hemodynamic measurement to determine an appropriate flow rate of PCPS. On day 3, ECG showed atrioventricular dissociation, marked widening of the QRS (Fig 1B), and frequent ventricular tachycardia. On day 4, chest radiography revealed worsened congestion of the lungs (Fig 2, middle). Echocardiography showed partial recovery of right ventricular contraction with persistently low left ventricular function (Fig 3). On day 5, QRS duration was shortened to 0.12 sec (Fig 1C). On day 7, the right ventricular contraction value returned to almost normal with a partial recovery of left ventricular function demonstrated by repeated echocardiography, and consequently the PCPS flow was reduced to 2.5 L/min. On day 10, the PCPS device was surgically removed. Just after removal, right ventricular contraction recovered to normal and the left ventricular ejection fraction was measured as 0.41 by echocardiography. On day 12, the IABP device was removed and the patient was extubated. The continuous drip infusion of vasopressor was discontinued on day 17.

On day 70, the ECG showed normal QRS interval, left-axis deviation, poor r progression in V1-3, and an inverted T in V1-3 (Fig 1D). Chest radiography showed a cardiothoracic ratio of 0.45 with no lung congestion (Fig 2, right). Cardiac catheterization was carried out on day 73. Normal coronary anatomy and a left ventricular ejection fraction of 0.44 were demonstrated by arteriography and left ventriculography. Right ventricular endomyocardial biopsy showed slight inflammatory infiltration, fibrosis, and some exfoliation of myocardium, which were compatible with the Dallas criteria for borderline myocarditis.9 The paired-sera titration of antibodies to virus disclosed no significant increase in titer. The patient was discharged on day 90, although she was taking 20 mg of furosemide and 0.125 mg of digoxin orally per day. There has been 18 months' follow-up, with echocardiographic data showing a left ventricular ejection fraction of 0.58 and an end-diastolic left ventricular dimension of 44 mm. The patient's activity level has completely returned to normal.

Case 2

A 34-year-old Chinese woman with profound hypotension and anuria was referred to our institution for advanced mechanical support. There was no past history of heart disease or of other critical disease. She had a regular menstrual cycle and no coronary risk factors. Two days before the referral, she had noted fever and mild dyspnea on exertion. On the next day, these symptoms exacerbated so rapidly that she visited a nearby hospital. The chest radiograph revealed severely congested lungs with mild cardiomegaly, and blood gas analysis showed severe hypoxemia. She was admitted to that hospital with a diagnosis of acute heart failure. Her hemodynamic status continued to deteriorate, although inotropic agents, respirator care, and IABP were initiated. She fell into cardiogenic shock with anuria, and 17 h after the admission she was transferred to our institute.

On admission to our coronary care unit, she was clearly conscious. Her temperature was 37.6°C, systemic blood pressure 73/34 mm Hg, and heart rate
Fig 4. Electrocardiogram of case 2 on admission (A), on day 3 (B), and on day 70 (C).

Fig 5. Time course of global right and left ventricular performance in case 2. Abbreviations are the same as for Fig 3.

Fig 6. Chest radiograph of case 2 on admission (left), on day 4 (middle), and on day 70 (right).
98 beats/min. ECG showed sinus tachycardia, poor r progression in leads V₁₋₄, low voltage in leads V₁₋₆, slight elevation of ST segment in leads aVL, V₁, and V₅, and ST depression in leads II, III, aVR, and V₆ (Fig 4A). Cardiac sonographic examination revealed normal chamber size but severe right and left ventricular global hypokinesis (Fig 5). Right-sided heart catheterization showed that the mean right atrial pressure was 18 mm Hg, pulmonary arterial pressure 35/28 mm Hg, mean pulmonary wedge pressure 29 mm Hg, and cardiac index 1.6 L/min per m². The CK level was 2488 IU/L with a myocardial band of 120 IU/L. Systolic blood pressure decreased to 40 mm Hg 10 min after admission; canulsa were inserted into the right femoral artery and vein for PCPS, and the position of the venous catheter tip was immediately checked by echocardiography. PCPS was initiated at a rate of 3.5 L/min in addition to the conventional treatments. To prevent blood coagulation, heparin was given continuously to ensure an activated clotting time of 150 sec in addition to continuous infusion of nafamostat mesilate (0.02–0.05 mg/kg per h).

In the patient's PCPS course, consumption thrombocytopenia occurred from day 3, exacerbation of lung edema on day 4 (Fig 6, middle), and hemolysis from day 6. ECG on day 4 showed poor r progression in leads V₁₋₄, OS in lead aVL, slight elevation of ST segment in leads aVL, V₁, and V₅, and ST depression in leads II, III, aVR, and V₄₋₆ (Fig 4B). Repeated echocardiography revealed that right ventricular function began to improve on day 4 and left ventricle from day 7 (Fig 5). On day 8, the PCPS flow was reduced to 2.0 L/min. PCPS was surgically removed on day 11. The patient was extubated on day 13 and IABP was removed on day 14. Continuous vasopressor drip infusion was discontinued on day 18. The patient's general condition recovered gradually after resolution of a left peroneal neuropathy. On day 70, chest radiography revealed normal cardiac size and no lung congestion (Fig 6, right), and ECG showed T inversion in leads 1 and V₃₋₆ (Fig 4C). There was no significant increase in virus-neutralizing antibody titer in paired serum. Unfortunately, we could not carry out cardiac catheterization or endomyocardial biopsy because the patient's husband refused. Although we had no pathologic documentation of acute myocarditis, the patient's clinical manifestations and hospital course were compatible with such as a diagnosis. The patient was discharged from our hospital on foot on day 139. Echocardiography on day 199 showed a left ventricular ejection fraction of 0.6 and an end-diastolic left ventricular dimension of 49 mm. Her condition has been uneventful for 13 months, without any drugs.

Discussion
These 2 cases demonstrate the clinical feasibility of heparin-bound PCPS for prolonged extracorporeal circulation in patients with acute severe myocarditis. A heparin surface immobilization treatment for the entire blood-contacting surfaces including a polypropylene microporous oxygenator has recently been developed to reduce the dose of systemic heparin required. Covalent binding of the amino residues in heparin to the plastic surfaces resulted in better thrombus resistance and biocompatibility than did the use of non-coated circuits by reducing the activation of the coagulation cascade, platelets, leukocytes, and the complement system. The PCPS that was used in our 2 patients utilizes a polyfunctional polymer with a high molecular weight polyethyleneimine as a spacer for heparin immobilization to increase the amount of heparin on the surfaces as well as heparin affinity for antithrombin III. Polyfunctional polymers have been proven to amplify the surface concentration of heparin by increasing the number of available reactive coupling sites. In order to achieve uniform surface bonding of heparin, in situ surface modification using ozone oxidation was also applied in our system. The patients' cardiac functions recovered very slowly, so that the PCPS was continued for more than 9 days; however, there were no critical problems with the clinical appearance of the heparin-bound PCPS except for a slight plasma leak that was found in the oxygenator in case 1 on day 11.

Serial biventricular functions were monitored by echocardiography, as shown in Figs 3 and 5. In case 1, biventricular failure progressed from right ventricular dysfunction. Mendes et al have reported that the detection of right ventricular dysfunction on echocardiography provides a clinical marker predictive of an adverse outcome of acute myocarditis. At present, PCPS is the most effective and a least invasive method of treating life-threatening right dominant acute biventricular heart failure! Our patients had transient exacerbation of lung congestion on day 4, even on PCPS. The possible explanations for this phenomenon are overhydration and earlier recovery of right ventricular performance than that of left ventricular performance. The recovery of left ventricular function in each case was delayed compared with that of right ventricle. Further improvement in left ventricular function was found even 90 days after admission without dilation of the chamber sizes. The marked reduction in preload brought about by the PCPS and the reduction in afterload by IABP during the acute phase of severe myocarditis may have contributed to the inhibition of

Japanese Circulation Journal Vol.61, December 1997
ventricular dilation.  

In using PCPS for patients with acute myocarditis, it is recommended that: (1) the PCPS is applied as soon as possible to avoid the progression of multiple organ damage to an irreversible state if circulatory insufficiency cannot be remedied by conventional treatments including IABP, especially in a patient with right ventricular severe dysfunction; (2) a sufficiently thromboresistant oxygenator and circuits tolerant against long-term use under low-dose systemic heparinization are selected; (3) a venous catheter tip is placed at the high lateral right atrium under 2-dimensional echo or X-ray guidance; and (4) IABP is used to reduce the afterload and to increase coronary arterial flow.  

In summary, 2 patients with acutely severe myocarditis were successfully treated by long-term use of heparin-binding PCPS, and their conditions have been uneventful for periods of longer than 12 months after discharge.

Acknowledgment

We express our appreciation to Kazuhiko Hagiwara for advice on the manuscript.

References