The Clinical Potential of Impella 5.0 Support in the Treatment of Recurrent Fulminant Viral Myocarditis with Profound Cardiogenic Shock

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Abstract:
We herein report the clinical potential of Impella 5.0 support, which is a catheter-mounted micro-axial left ventricular support device, in a 39-year-old man with recurrent fulminant viral myocarditis complicated with profound cardiogenic shock despite inotropic infusion and an intra-aortic balloon pumping. Switching from these therapies to the Impella 5.0 device provided sufficient systemic perfusion with well-controlled left ventricular diastolic properties to facilitate a prompt recovery from profound cardiogenic shock. The patient was uneventfully discharged on the 27th hospital day. Given its effect of cardiac protection with sufficient systemic perfusion, the Impella device should be considered the first-line therapy for the treatment of fulminant myocarditis complicated with cardiogenic shock.

Key words: recurrent fulminant myocarditis, cardiogenic shock, Impella, left ventricular unloading

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Introduction
Fulminant myocarditis, defined as the presence of severe hemodynamic compromise requiring parenteral inotropic or mechanical circulatory support, carries an extremely high risk of fatal outcomes, accounting for 40% of in-hospital deaths in the acute phase (1, 2). Mechanical circulatory support using an intra-aortic balloon pumping and/or veno-atrial extracorporeal membrane oxygenation has been widely applied for cardiogenic shock due to fulminant myocarditis in Japan (3). In mid-2017, as an additional circulatory support device, the Impella device (Abiomed, Danvers, USA) (4), which is a catheter-mounted micro-axial left ventricular support device, was launched in Japan.

We herein report the clinical potential of Impella 5.0 (5.0 l/min) support in a 39-year-old man with recurrent fulminant viral myocarditis complicated with profound cardiogenic shock despite inotropic infusion and intra-aortic balloon pumping. Our assessment of the serial hemodynamic profiles of the patient before and after Impella 5.0 support may highlight the clinical advantages of the Impella device in patients with this critical disorder.

Case Report
A 39-year-old man was referred to our institute for the evaluation of elevated plasma levels of cardiac enzymes with ST-segment elevation in his electrocardiogram.

Two weeks earlier, the patient had been treated for vomiting and diarrhea with a diagnosis of viral enteritis by his medical practitioner. Three days before admission to our institute, the patient was admitted to another hospital for the treatment of a sustained low-grade fever and epigastralgia.

On admission to our institute, his temperature was 36.5°C, and his blood pressure was 95/69 mmHg with a regular
pulse rate of 86/minute. A 12-lead electrocardiogram showed the first-degree atrial-ventricular block and right-bundle-branch-block with ST segment elevation in the left precordial leads (Fig. 1A), and an echocardiogram revealed an ejection fraction of 20% with diffuse left ventricular hypokinesis. The plasma levels of creatine kinase were 1,002 U/L (normal range, 30-200), and troponin-T was 4.86 ng/mL (normal <0.014). The patient had a history of intensive treatments for fulminant viral myocarditis in our institute five years earlier. An endomyocardial biopsy on admission revealed broad infiltrating lymphocytes and myocytolysis (Fig. 1B), resulting in a diagnosis of recurrent fulminant viral myocarditis.

The patient was started on a low dose of dobutamine on admission, followed by the addition of norepinephrine with intra-aortic balloon pumping the next day. Despite these intensive therapies, the cardiac power output, which equated to the cardiac external work per minute and was calculated as the product of the simultaneous cardiac output and mean arterial pressure (5), demonstrated a gradual decrease from 0.5 to 0.3 watts with a steep increase in atrial lactate levels from 1.6 to 5.1 mmol/L. As indices of left ventricular diastolic properties, the diastolic pulmonary artery pressure (substitute for the mean left atrial pressure) and mean right atrial pressure were increased by over 20 mmHg.

Under a diagnosis of fulminant viral myocarditis with profound cardiogenic shock, switching from intra-aortic balloon pumping with inotropic infusion to Impella 5.0 support was performed on the third hospital day (Fig. 2A and B). Impella 5.0 support rapidly increased the cardiac power output to 0.8 watts with a prompt normalization of atrial lactate levels and well-controlled diastolic pulmonary artery pressure and mean right atrial pressure (Fig. 2C). The addition of intravenous immunoglobulin treatment (1.5 g/kg×2 days) with Impella 5.0 support was also decided by our heart team. Impella 5.0 support was gradually terminated with stabilized hemodynamics and the normalization of plasma levels of cardiac enzymes on day 7. Two days before the patient was discharged, a high neutralizing antibody titer of 4,096 against Echovirus was detected. The patient ultimately fully recovered and was discharged from our institute on the 27th hospital day with a final left ventricular ejection fraction of 36% with the administration of beta-blocker and angiotensin-converting enzyme inhibitor.

Discussion

We report the dramatic hemodynamic profiles after switching from intra-aortic balloon pumping with inotropic infusion to Impella 5.0 support in a patient with recurrent fulminant viral myocarditis with profound cardiogenic shock. The present case may imply the clinical advantages of the early adoption of an Impella 5.0 device in patients with this critical disorder.

Three different types of mechanical circulatory support devices have been available to support acute hemodynamic compromise in Japan since mid-2017: intra-aortic balloon pumping, veno-atrial extracorporeal membrane oxygenation, and the Impella device. As shown in Fig. 2B, the Impella device is positioned across the aortic valve (cannula) to work as a micro-axial rotary pump (motor housing), expelling aspirated blood from the left ventricle (inlet area) to the ascending aorta (outlet area) under the automated Impella controller (differential pressure sensor) (4, 6). Veno-atrial extracorporeal membrane oxygenation has been utilized as a mechanical circulatory pump with the capacity to provide sufficient cardiac output with systemic oxygenation. However, this method of support increases the left ventricular oxygen demand due to an increase in the left ventricular afterload and this sometimes causes left ventricular thrombosis due to the inhibition of the ejection blood flow (7). In contrast, the Impella device increases the systemic circulatory perfusion by decreasing the left ventricular work, known as left ventricular unloading, thereby ameliorating the myocardial oxygen supply/demand ratio and improving the myocardial mechanical efficacy (8). At the first episode of fulminant viral myocarditis in the present case, circulatory sup-
The pressure of around 60 mmHg under intensive inotropic support above 0.53 watts, in contrast to the actual mean blood mmHg was required in order to keep the cardiac power output full support of Impella 2.5, a mean blood pressure of 95 Impella 2.5 was insufficient in the present case. With the pan in 2018, we chose Impella 5.0 because the power of (2.5 L/min) and Impella 5.0 (5.0 L/min) are available in Ja- the need for any inotropic support. While both Impella 2.5 keeping all other hemodynamic parameters stable without pella 5.0 promptly improved the cardiac power output whileately afterwards, dropping far below the cut-off value. Im- intra-aortic balloon pumping; however, it worsened immedi- the initiation of inotropic therapy on admission, followed the present case. The value was improved temporarily after diogenic shock with a cut-off value of 0.53 watts (5), was been used.

The cardiac power output, which is reportedly the strong- est index for predicting in-hospital mortality in cases of cardiogenic shock with a cut-off value of 0.53 watts (5), was extremely useful for assessing the serial hemodynamics in the present case. The value was improved temporarily after the initiation of inotropic therapy on admission, followed intra-aortic balloon pumping; however, it worsened immedi-ately afterwards, dropping far below the cut-off value. Imp- ella 5.0 promptly improved the cardiac power output while keeping all other hemodynamic parameters stable without the need for any inotropic support. While both Impella 2.5 (2.5 L/min) and Impella 5.0 (5.0 L/min) are available in Ja-pan in 2018, we chose Impella 5.0 because the power of Impella 2.5 was insufficient in the present case. With the full support of Impella 2.5, a mean blood pressure of 95 mmHg was required in order to keep the cardiac power output above 0.53 watts, in contrast to the actual mean blood pressure of around 60 mmHg under intensive inotropic sup- port. Based on the concept of curing the heart while maintain- ing a state of rest in the setting of viral myocarditis, we believe that the Impella device should be considered to be a first-line mechanical circulatory support device for the treat- ment of fulminant myocarditis with cardiogenic shock.

Due to the absence of a sensitive non-invasive diagnostic modality for detecting viral myocarditis, there are no large population-based, epidemiological studies involving the clinical assessment of viral myocarditis (9). Acute viral myocarditis sometimes revealed a self-limited recovery without any symptoms, while at other times it can cause pro- gressive cardiac damage, leading to features of dilated cardiomyopathy (1, 2). In the present case, the left ventricular ejection fraction was 48% when the patient was discharged after the first hospitalization, a value that was maintained until the present hospitalization. A persistent viral infection in the myocardium may be associated with progressive myocardiomyopathy (1, 2), while the incidence of recurrent viral myocarditis is quite low (12).

A total of seven case studies, including the present pa- tient, have reported recurrent viral myocarditis with virus identification (12-17) (Table). Surprisingly, four of these seven patients showed fulmination. Fulminant viral myo- carditis is a clinicopathological classification presenting with rapid hemodynamic deterioration, thereby resulting in card- iogenic shock with fatal clinical outcomes. In contrast to the findings of a previous small cohort study (18) reporting

**Figure 2.** A: Chest X-ray findings with the deployment of the Impella 5.0 device. B: The composition of the Impella 5.0 device in the patient. C: Hemodynamic profiles before and after Impella 5.0 support. MAP: mean arterial pressure, PAdiast: diastolic pulmonary atrial pressure, RAP: mean right atrial pressure, CO: cardiac output, COP: cardiac power output (calculated as MAP × CO/451), CCU: cardiac care unit, IABP: intra-aortic balloon pumping, Impella 5.0 P-level: 0 to 9 (highest number indicating maximal support), DOB: dobutamine, Nadr: noradrenaline, mcg: microgram, IVIG: intravenous immunoglobulin, LVEF: left ventricular ejection fraction
a long-term benign prognosis of fulminant myocarditis after the acute critical phase, a recent clinical study indicated worse long-term clinical outcomes with advanced cardiac dysfunction in such cases (19). Experimental studies have proposed several potential mechanisms underlying the pathogenesis of viral myocarditis, in which myocardial injury might be mediated through initial viral toxicity and thereafter the cellular immune response, resulting in persistent viral infection (2). However, precisely why viral myocarditis rarely shows recurrence and/or is occasionally fulminated remains unclear. The three instances of recurrence in four of the seven patients in Table underscore the need to follow the clinical features of the present patient carefully. Future basic and clinical studies must attempt to address these complex issues in order to improve the clinical outcomes of this critical disorder.

In conclusion, we herein report the clinical potential of Impella 5.0 support in the treatment of recurrent fulminant myocarditis with profound cardiogenic shock. Given its effect of cardiac protection with sufficient systemic perfusion, the Impella device should be considered the first-line therapy for the treatment of this critical disorder.

The authors state that they have no Conflict of Interest (COI).

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Table. Case Studies of Recurrent Viral Myocarditis.

| published year (ref.) | sex | age, year | fulminant | age, year | fulminant | type of virus | clinical outcomes |
|-----------------------|-----|-----------|-----------|-----------|-----------|--------------|------------------|
| 2003 (12)             | male | 75        | no        | 75        | yes       | Influenza    | death            |
| 2011 (13)             | female | 29, 36    | no, no    | 37        | no        | Coxsackie    | alive            |
| 2012 (14)             | female | 5, 7      | yes, no   | 8         | yes       | Influenza    | death            |
| 2014 (15)             | male | 36, 40    | yes, no   | 52        | yes       | Influenza    | alive            |
| 2018 (16)             | female | 14        | no        | 15        | no        | Parvo       | alive            |
| 2018 (17)             | female | 25, 27    | no, no    | 28        | no        | Erythro     | alive            |
| our case              | male | 34        | yes       | 39        | yes       | Echo        | alive            |

ref.: reference number