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Original Article

Possibility of an Intra-Aortic Balloon Pump as a Bridge Therapy to Recovery for Septic Cardiomyopathy

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ABSTRACT

Introduction: Myocardial damage is reported in about 20% to 60% of sepsis cases. The circulatory system in early sepsis is hyperdynamic in state, but with time, cardiac function decreases and shifts toward cardiogenic shock. This study aimed to determine whether an intra-aortic balloon pump (IABP) could be an effective cardiac support for septic cardiomyopathy.

Methods: Twelve patients with septic cardiomyopathy who were screened between April 2010 and March 2016 in the Saiseikai Yokohamashi Tobu Hospital Emergency and Critical Care Center were enrolled retrospectively for this observational study. Hemodynamics was evaluated using the following parameters: mean blood pressure; heart rate; catecholamine index; and serum lactate level. These parameters were compared before IABP insertion and at 24 and 72 hours after insertion. Cardiac function was assessed by evaluating the N-terminal pro b-type natriuretic peptide (NT-pro BNP) and left ventricular ejection fraction (LVEF) at days 0, 3, and 7 after intensive care unit admission.

Results: The mean blood pressure tended to increase, the heart rate significantly decreased, and the catecholamine index and serum lactate levels decreased significantly after IABP insertion. Nine of the 12 patients survived and showed improved LVEF, which returned to the normal range during the follow-up period.

Conclusions: From our experience of 12 cases, we suggest that IABP may be used for septic cardiomyopathy.

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KEYWORDS: sepsis, cardiomyopathy, cardiac support device

Introduction

Treatment for sepsis/septic shock has recently been standardized.[1,2)] However, in cases of sepsis, the problem is not resolved, and serious complications may arise, despite standard treatments. Septic cardiomyopathy, where sepsis

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is accompanied by myocardial injury occurs in 20% to 60% of sepsis cases.[3] The mechanism of septic cardiomyopathy involves suppression of the myocardium due to the systemic circulation, and changes in the microcirculation, autonomic nervous disorders, and inflammation. Among the inflammatory mediators produced in septic cardiomyopathy, the overproduction of inflammatory cytokines is thought to play a major role in the pathogenesis of cardiomyopathy. The pathogenesis of septic shock involves increased warmth in the periphery owing to lower vascular resistance caused by vasodilators, such as nitric oxide, which is produced excessively in the early stages. This is followed by the development of a pathological condition called the hyperdynamic state, where cardiac output is increased. As this stage progresses, both cardiac function disorders and vascular endothelial cell disorders are observed. This marks failure of the peripheral circulation. This condition is likely to cause cardiogenic shock, and a mechanical cardiac support device is considered when drugs fail to improve the hemodynamics. We considered that IABP improved the hemodynamic parameters in septic shock patients with cardiomyopathy as in the case of cardiogenic shock patients. Although there are reports of the usefulness of veno-arterial extracorporeal membrane oxygenation (ECMO) for refractory septic cardiomyopathy,[4,5] there are only a few reports and case series of the use of an intra-aortic balloon pump (IABP) for septic cardiomyopathy.[6–8] There are no clear criteria of cardiac support devices for septic cardiomyopathy. The purpose of this study was to investigate whether cardiac support provided by IABP was effective for septic cardiomyopathy in the cases where medication did not improve the patient's hemodynamic condition. In addition, we examined in which patients IABP was effective, and in which cases it was invalid and ECMO should be introduced.

Methods

This was a retrospective observational study conducted at a single center. We examined the records of patients who had presented with septic shock to the Emergency and Critical Care Center at Saiseikai Yokohamashi Tobu Hospital between April 2010 and March 2016. Cases in which conventional treatment had failed and an IABP was inserted were considered. Patients aged < 20 years, with cardiopulmonary arrest, or with a "do not attempt resuscitation order," were excluded. Treatment for septic shock was carried out if there was a surgical or drainage site at the source of infection, and antibiotics were administered. If the circulation did not improve on treatment with fluids and vasopressor/inotropic drugs (epinephrine > 0.3 μg/kg/min or dobutamine > 5 μg/kg/min + norepinephrine > 0.3 μg/kg/min), sustained steroid (hydrocortisone 200 mg/day) was administered, along with polymyxin B-immobilized fiber column-direct hemoperfusion (PMX-DHP). The IABP was inserted in cases with deteriorated cardiac function and prolonged shock (mean blood pressure (mBP) < 65 mmHg, serum lactate level > 18 mg/dL and left ventricular ejection fraction (LVEF) < 40%) despite administration of these treatments. The IABP was inserted from the left or right femoral artery, and a balloon capacity of 40 ml for patients with a height ≧165 cm, and 34 ml for patients with a height <165 cm was selected. When the shock was reversed (mBP > 65 mmHg, serum lactate level < 18 mg/dL) with catecholamines (dobutamine < 5 μg/kg/min and norepinephrine < 0.1 μg/kg/min), IABP support was decreased from 1:1 to 1:2. The IABP was removed when the hemodynamics were stable. To determine the effect of the IABP, the kinetic parameters of circulation, including the mBP, heart rate (HR), serum lactate level, and catecholamine index (CAI: dobutamine [μg/kg/min] + epinephrine [μg/kg/min] × 100 + norepinephrine [μg/kg/min] × 100) were compared before IABP insertion and at 24 and 72 hours after insertion.

Cardiac function was assessed by evaluating the LVEF and serum N-Terminal pro-brain natriuretic peptide (NT-pro BNP). Those were compared at days 0, 3, and 7 after intensive care unit (ICU) admission. LVEF was evaluated by the M-mode method on transthoracic ultrasound cardiography (UCG).

The severity of sepsis was determined by the acute physiology and chronic health evaluation (APACHE) II score and the sequential organ failure assessment (SOFA) scores. APACHE II score was obtained by adding the worst values within 24 hours of ICU admission. The mortality rate was 73% if the APACHE II score was 30-34 and 84% if it was ≧35.[9] The SOFA score is an index created for the purpose of assessing the degree of damage to organs. The SOFA score is a score of 0-4 for 6 items: respiration, coagulation, liver function, circulation, central nervous system, and renal function. The mortality rate is ≦ 33% if the SOFA score is ≦9, and 95% if the SOFA score is ≧11.[10]

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama,

Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of the R commander designed to add statistical functions frequently used in biostatics.[11]

Non-parametric analysis was performed for continuous variables that showed non-normal distribution. Owing to the small number of cases, continuous variables were compared using the Friedman test. Statistical significance was defined as a *P*-value of less than 0.05. The study protocol was approved by the Ethics Committee of Saiseikai Yokohamashi Tobu Hospital (No. 2018028).

Results

We analyzed 12 cases where an IABP was inserted for septic cardiomyopathy within the observation period. No ST-T changes were seen on the electrocardiogram in all patients from admission, and there were no findings suggestive of Takotsubo cardiomyopathy or acute myocarditis. The patient characteristics are shown in Table 1. The median age was 71 years, and 75% were male. Two patients had a history of ischemic heart disease, but their left ventricular function was within the normal range. There were no immunocompromised patients. Infection was mostly attributed to respiratory causes (6 of 12 patients). The study patients' clinical characteristics are shown in Table 2. The median duration of IABP support was five days. Fifty-eight per cent of the patients received PMX-DHP, while 83% received continuous renal replacement therapy. There were no complications by IABP insertion. Nine of the 12 patients survived. Two patients (No. 2 and No. 7) died from multiple organ failure, and one (No. 12) died from a secondary infection. Two patients (No. 7 and No. 9) needed VA-ECMO. One patient developed complications of atrial fibrillation, while another developed cardiac arrest. Patients who used VA-ECMO were excluded from comparison of the hemodynamic parameters, LVEF, and NT-pro BNP before and after IABP insertion because this treatment directly affects the hemodynamics. As shown in Fig. 1, the median (range) mBP 64 mmHg (50-90 mmHg) before IABP insertion tended to increase to 84 mmHg (74-100 mmHg) at 24 hours and 80 mmHg (70-109 mmHg) at 72 hours, but this was not statistically significant ($P = 0.196$). The median (range) HR 90/min (60-129/min) before IABP insertion decreased significantly to 77/min (65-110/min) at 24 hours and 70/min (60-88/min) at 72 hours ($P = 0.002$). The median (range) CAI of 27 μg/kg/min (20-65 μg/kg/min) before IABP insertion decreased significantly to 6 μg/kg/min (3-35 μg/kg/min) at 24 hours and 0 μg/kg/min (0-20 μg/kg/min) at 72 hours ($P < 0.001$). The median (range) serum lactate level was 36 mg/dL (13-102 mg/dL) before IABP insertion and decreased significantly to 13 mg/dL (6-56 mg/dL) at 24 hours and 11 mg/dL (7-22 mg/dL) at 72 hours ($P < 0.001$). As shown in Fig. 2, the median (range) LVEF 28% (20%-32%) at day 0 after ICU admission increased significantly to 40% (25%-55%) at day 3 and 45% (30%-64%) at day 7 ($P < 0.001$). The LVEF was normalized within 15 days after admission to the ICU in all eight patients who survived without VA-ECMO (Table 1). Furthermore, one patient who survived with VA-ECMO (Patient No. 9 in Table 1) had a normal LVEF of 70% 14 days after admission to the ICU. The median (range) NT-pro BNP of 6411 pg/mL (2787-35000 pg/mL) at day 0 after ICU admission was not significantly different, with 3183 pg/mL (1002-35000 pg/mL) at day 3 and 4040 pg/mL (870-5798 pg/mL) at day 7 ($P = 0.183$).

Discussion

Dobutamine, a selective β1 receptor agonist, is an inotropic drug recommended in sepsis guidelines.[1] However, cardiac dysfunction caused by sepsis may not be improved with dobutamine.[12–15] The concentration of catecholamine in circulating blood is increased during sepsis and chronic heart failure,[16, 17] and a decrease in the number of β receptors in the myocardium has been reported.[18–20] Patients enrolled in this study were also managed for infected focus and were treated with appropriate antibiotics; however, the septic shock could not be resolved despite high doses of vasopressors and inotropic drugs. This study showed that after the IABP insertion, mBP tended to increase, HR significantly decreased, and the CAI and serum lactate level decreased significantly, compared to before IABP insertion. The main effect of IABP is an increase in the mean arterial pressure owing to increased diastolic blood pressure, increased coronary blood flow, and reduced afterload. In this way, IABP improved hemodynamic parameters in septic shock with cardiomyopathy as in the case of cardiogenic shock patients. A few studies have reported that there was no prognostic improvement in myocardial infarction in cases accompanied by cardiogenic shock,[21] but some studies have also reported that IABP may have a therapeutic effect in patients with severe heart failure that do not respond to the above medical treatment. Septic shock patients within this study had lower mortality when their severity was ad-

Table 1 Characteristics of the 12 septic shock patients

Patient (No)	Age (years)	Gender	Body mass index (kg/m^2)	Diabetes mellitus	Cancer	Collagen disease	Immunodeficiency	Ischemic heart disease	Atrial fibrillation	Cardiopulmonary arrest	Infection	APACHE II score	SOFA score	mBP (mmHg)	HR (bp/min)	CRP (mg/dL)	Bilirubin (mg/dL)	Creatinine (mg/dL)	Procalcitonin (ng/mL)	LVEF (%) / Days	Complication	ICU stay, (days)	Hospital stay, (days)	Survival
1	67	male	20.7	+	-	-	-	-	-	-	Cellulitis	33	12	59	110	51.70	1.2	2.46	100.00	64 / 14	-	17	62	+
2	69	male	27.5	+	-	-	-	+	-	-	unknown	42	17	65	90	9.10	2.2	3.11	12.70	58 / 12	-	18	18	-
3	86	female	22.1	+	-	-	-	-	-	-	Peritonitis	26	10	80	98	24.70	1.0	0.58	3.64	62 / 15	-	16	37	+
4	59	male	19.6	-	-	-	-	-	-	-	Pneumonia	29	8	83	60	1.90	0.5	0.78	0.05	60 / 10	-	13	28	+
5	78	female	19.4	-	-	-	-	-	-	-	Pneumonia	42	18	90	80	4.60	2.4	3.63	6.95	65 / 11	-	15	60	+
6	78	male	18.1	-	-	-	-	-	-	-	Pneumonia	43	15	80	80	23.82	0.4	4.78	0.36	62 / 13	-	14	45	+
7	36	male	26.0	-	-	-	-	-	-	+	Pneumonia	24	19	50	140	15.40	4.4	1.86	100.00	45 / 10	-	11	11	-
8	86	male	17.3	-	-	-	-	-	-	-	Pneumonia	36	12	50	90	20.10	1.1	1.70	0.76	57 / 9	-	10	68	+
9	49	male	24.4	-	Colon	-	-	-	+	-	Peritonitis	34	10	54	120	1.39	0.8	1.46	87.64	70 / 14	-	20	56	+
10	49	female	18.7	-	-	-	-	-	-	-	Pneumonia	15	14	56	129	11.50	1.2	1.19	60.83	60 / 15	-	15	48	+
11	81	male	21.3	+	-	-	-	+	-	-	Colitis	28	12	63	90	23.50	3.0	1.50	257.00	63 / 11	-	15	33	+
12	73	male	22.0	+	-	-	-	-	-	-	Cellulitis	27	14	60	90	28.20	1.1	1.38	50.00	57 / 11	-	22	22	-

APACHE II: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment;
mBP: mean blood pressure; HR: heart rate; CRP: C-reactive protein; ICU: intensive care unit; LVEF: left ventricular ejection fraction; Days: the number of days from ICU admission until performance of ultrasound cardiography

Table 2 Clinical characteristics of the 12 patients at the time of IABP insertion

APACHE II, median (range)	31 (15-43)
SOFA, median (range)	13 (8-19)
Mean blood pressure, mmHg, median (range)	62 (50-90)
Heart rate, /min, median (range)	90 (60-140)
Central venous pressure, mmHg, median (range)	14 (6-20)
Cardiac index, median (range)	1.6 (1.3-2.0)
Left ventricular ejection fraction,%, median (range)	28 (18-32)
Catecholamine index, μg/kg/min, median (range)	30 (20-65)
pH, median (range)	7.269 (7.082-7.509)
Lactate, mg/dl, median (range)	43 (13-150)
C-reactive protein, mg/dl, median (range)	17.75 (1.39-51.70)
Procalcitonin, ng/ml, median (range)	31.35 (0.05-257)
N-Terminal pro-brain natriuretic peptide, pg/ml, median (range)	6411 (2787-35000)
White blood cell count, $\times 10^3/\mu L$, median (range)	9.86 (1.00-27.62)
Hemoglobin, g/dl, median (range)	13.8 (9.0-16.7)
Platelet count, $\times 10^4/\mu L$, median (range)	11.3 (3.7-33.1)
IABP insertion days, median (range)	5 (3-7)
PMX-DHP, n (%)	7 (58)
CRRT, n (%)	10 (83)
Steroid, n (%)	9 (75)

SOFA: sequential organ failure assessment
APACHE II: acute physiology and chronic health evaluation
PMX-DHP: polymyxin B-immobilized fiber column-direct hemoperfusion
CRRT: continuous renal replacement therapy

justed with APACHE II score or SOFA score. This may contribute to decreasing mortality due to circulatory failure in the acute phase. Two of the cases in this study required VA-ECMO. One case had extremely low cardiac function. The flow support of the IABP is about 30% of the cardiac output, which may be insufficient in cases where the cardiac function is extremely low. In another patient with atrial fibrillation, IABP balloon dilation could not be timed and might not be effective. Nakamura et al. in their study reported that IABP was not effective in patients with septic shock accompanied by arrhythmia and tachycardia (HR $>$ 150/min).[6] In cases with accompanying arrhythmia, the IABP balloon expansion becomes poor, and the required effect may be insufficient. We thought that patients who nearly approached cardiac arrest, or those who had complications with arrhythmias may have had insufficient IABP support. In these cases, rather than IABP, we thought VA-ECMO should be considered from the beginning. From our experience of 12 cases, IABP should be considered as the first choice of cardiac support device for patients with LVEF ≧20% and no arrhythmia. Further, in recent years, the Impella® (Abiomed, Danvers, Massachusetts) has become available as a left ventricular assist device. Impella®, which is percutaneously placed inside the left ventricle, is used as a cardiac assist device in cardiogenic shock, where it can assist cardiac output from 2.5 L/min to 5.0 L/min. In cases of acute myocardial infarction, studies indicate it is not useful when compared to IABP,[22, 23] but it may be considered in the future for myocardial injury in sepsis as well as IABP. However, the indication should be considered cautiously owing to the high cost and the complications of hemolysis and bleeding.

There were no clear diagnostic criteria for septic cardiomyopathy, which is a myocardial disorder characterized by left ventricular dilatation, decreased left ventricular contractility, and natural recovery with progress. Septic cardiomyopathy is distinguished from Takotsubo cardiomyopathy.[24] It results in left ventricular diffuse hypokinesis. Many inflammatory cytokines are involved in septic cardiomyopathy, and mitochondrial dysfunction is also involved.[25–28] On the other hand, Takotsubo cardiomyopathy typically occurs when the contractile function of the mid to apical segments of the left ventricle is depressed and there is hyperkinesis of the basal walls. Takotsubo cardiomyopathy is accompanied by myocardial and systemic inflammation, with myocardial macrophage infiltration and acute proinflammatory monocyte and cytokines.[29] For patients in this study, the left ventricular contractility im-

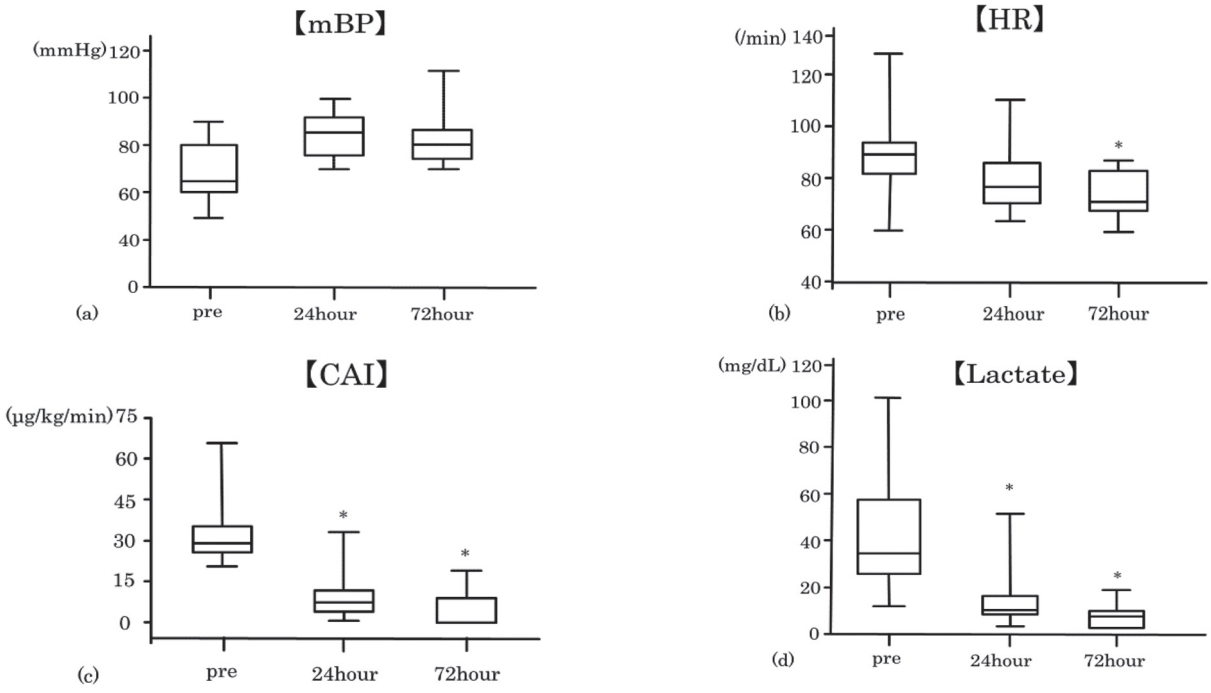

Fig. 1 Hemodynamic parameters before and after IABP insertion.
The bars represent median, the boxes are interquartile range, and the whiskers stand for minimum to maximum.
Statistics: Friedman test (N = 10). Bonferroni post-hoc test for comparison with pre IABP insertion. * $P<0.05$
(a): There was no difference in mean blood pressure (mBP) between pre and post IABP insertion.
(b): Heart rate (HR) was significantly decreased at 72 hours after IABP insertion compared with pre IABP insertion ($P = 0.002$).
(c): Catecholamine index (CAI) was significantly decreased at 24 and 72 hours after IABP insertion compared with pre IABP insertion ($P<0.001$).
(d): Lactate was significantly decreased at 24 and 72 hours after IABP insertion compared with pre IABP insertion ($P<0.001$).

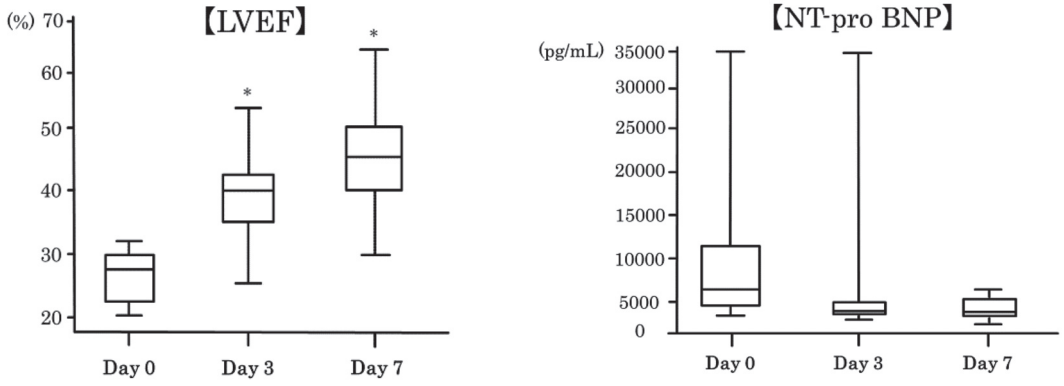

Fig. 2 LVEF and NT-pro BNP after ICU admission.
The bars represent median, the boxes are interquartile range, and the whiskers stand for minimum to maximum.
Statistics: Friedman test (N = 10). Bonferroni post-hoc test for comparison with Day 0. * $P<0.05$
LVEF was significantly increased at Day 3 and Day 7 compared with Day 0 ($P<0.001$).

proved after the acute phase of infection. All surviving patients showed improved LVEF, which returned to the normal range during the follow-up period. As the pathology is reversible, IABP is considered as an effective cardiac sup-

port device as a bridge therapy until cardiac function improves. Septic cardiomyopathy reports suggested that cardiac function improved within 7-10 days.[30] In our study, the period of improvement in cardiac function was similar to that generally reported. However, in some patients, LVEF was already normalized at day 3 after ICU admission. This is because catecholamines can be reduced by IABP, and it is possible that high dose catecholamine stimulation disappeared and recovery of myocardial function was accelerated.

As these cardiac support devices are only supporting therapy, basic sepsis management is required. Priority is given to rapid control of the source of infection and the management of inflammation. Randomized control trials are warranted to analyze if IABP provides useful circulatory support in prolonged circulatory disorders where septic cardiomyopathy is present.

Limitations

This study has some limitations. First, it is a retrospective study with a small sample size. Second, there is a potential bias in the selection of patients described here, especially as the decision for insertion of IABP or VA-ECMO was decided appropriate by the attending physician in the absence of a specific protocol. Third, the patients in this study used IABP in all cases and were not comparable to patients who did not use IABP.

Conclusion

From our experience of 12 cases, we suggest that IABP may be used as a bridge therapy for septic cardiomyopathy. IABP may be indicated except in patients with arrhythmia or extremely low cardiac function.

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Conflicts of interest: None declared.

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