REVIEW
Korean Circulation J 2005;35:563-572

ISSN 1738-5520

Mechanical Circulatory Supports in the Treatment of Fulminant Myocarditis

Joong-Il Park, MD[1] and Eun-Seok Jeon, MD, PhD[2]

[1]Division of Cardiology, Cardiac and Vascular Center, Seoul Veterans Hospital, Seoul, [2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ABSTRACT

Background and Objectives : Although fulminant myocarditis (FM) is known as a fatal disease, once patients have recovered, with aggressive pharmacologic therapy and/or mechanical circulatory supports (MCS), including intra-aortic pump, temporary ventricular assist device and percutaneous cardiopulmonary support, they may return to normal life with an excellent long-term prognosis. Elevated C-reactive protein, Creatinine phosphokinase and cytokine concentrations, decreased left ventricular ejection fraction and intraventricular conduction disturbances on admission may predict the progress of acute myocarditis to fulminant course. Early MCS helps save life and prevent multi-organ failures in patients with FM. The type of MCS may not affect the outcome of the clinical course when its complications are managed properly. Since other managements with immunoglobulin, antiviral agent or monoclonal antibody remain to be confirmed, aggressive hemodynamic support with MCS is the best management for patients with FM, who once recovered from the acute phase can return to normal life. **(Korean Circulation J 2005;35:563-572)**

KEY WORDS : Myocarditis ; Prognosis ; Mechanical circulatory supports.

Introduction

Approximately 10 percent of patients with recent onset cardiomyopathy, who undergo an endomyocardial biopsy, have lymphocytic myocarditis, which may be caused by viral infection.[1-3] The clinical course of patients with lymphocytic myocarditis varies; some patients have a subclinical disease, some present with a fulminant disease, which is frequently fatal, and others have an indolent disease that progress to dilated cardiomyopathy.[4-7] Lieberman et al.[8] classified myocarditis as either fulminant or acute (nonfulminant) on the basis of the clinicopathological criteria, including the severity of the illness on presentation. Paradoxically, patients with fulminant myocarditis (FM), although more severely ill on presentation, were more likely to recover left ventricular function than those with acute myocarditis. The survival rate of FM at 12-year was significantly better than that of acute myocarditis (93 vs. 45%, Fig. 1). Therefore, aggressive hemodynamic support is warranted for patients with FM that is a distinct clinical entity, with an excellent long-term prognosis.[9] Supporting this observation, there are several reports of patients with FM whose ventricular dysfunction resolved after aggressive pharmacologic support and/or mechanical circulatory support (MCS), such as intra-aortic balloon pump (IABP), temporary ventricular assist device (VAD) and percutaneous cardiopulmonary support (PCPS).[9-19] Since the risk of death during the acute phase is high, a bridge to recovery with circulatory support devices is often useful in FM patients. However, the type of device, technique of implantation and explantation, in addition to weaning protocol, remain unclear.[20] Moreover, despite of the excellent prognosis of FM, it is impossible to predict when patients with acute myocarditis may progress to FM,[21] but the predictors of FM on admission remain to be elucidated.[22-24]

In this review article, the author would like to summarize the clinical features of FM, review the prognostic factors and predictors, and introduce guidelines of MCS for the treatment of patients with FM.

Correspondence : Eun-Seok Jeon, MD, PhD, Department of Medicine, Sungkyunkwan University School of Medicine, Cardiac and Vascular Center, Samsung Medical Center, 50 Il-wondong, Kangnam-gu, Seoul 135-710, Korea
Tel: 82-2-3410-3448, Fax: 82-2-3410-3849
E-mail: esjeon@smc.samsung.co.kr

Definition, Incidence and Etiology of Fulminant Myocarditis

Lieberman et al.[8] reported a new clinicopathological

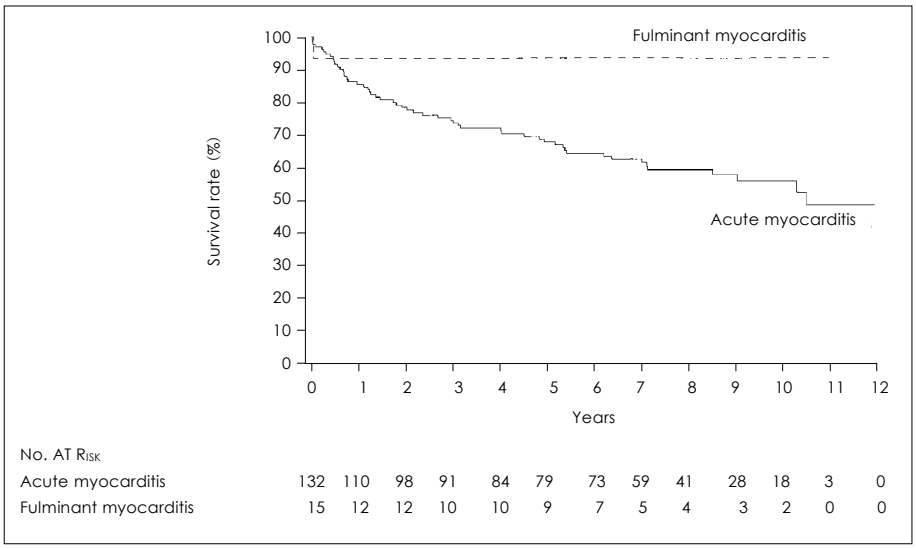

Fig. 1. Unadjusted transplantation-free survival according to the clinicopathological classification. Patients with fulminant myocarditis were significantly less likely to die or require heart transplantation during follow-up than those with acute myocarditis (p=0.05 by the log-rank test) (adapted from reference 9).

classification of myocarditis, with four distinct subgroups, by analysis of the histological findings and clinical course of the myocarditis. Patients with FM become acutely ill after a distinct viral prodrome, have severe cardiovascular compromise, multiple foci of active myocarditis on histological study and ventricular dysfunction, which either resolves spontaneously or results in death. McCarthy et al.[9] defined FM as the patients who had severe hemodynamic compromise that requires high doses of vasopressors (>5 μg of dopamine or dobutamine per kilogram of body weight per minute) or a left ventricular assist device. In addition, at least two of the following clinical features have to be present for histopathologically borderline or active myocarditis to be classified as fulminant: fever, distinct onset of symptoms of heart failure (fatigue, dyspnea on exertion or at rest, or edema that could be dated specifically to a one-to-two-day period), and a history consistent with the presence of a viral illness within the two weeks before hospitalization. In their report, only 15 out of 147 patients with myocarditis in pathology were FM.

The actual incidence of acute myocarditis has declined over time in the USA. In contrast, the incidence of FM has remained stable over time.[25] Moreover, both the absolute number and the proportion of cases of acute myocarditis from biopsies have declined over time (1985-1996). In contrast, the number and proportions of FM cases has remained relatively stable, as shown in Fig. 2.[9] The reason for this stability is unclear. In Korea, there are only case reports of acute viral myocarditis,[12][26-28] however, no surveillance data for the incidence of enteroviral infection with or without myocarditis are available.

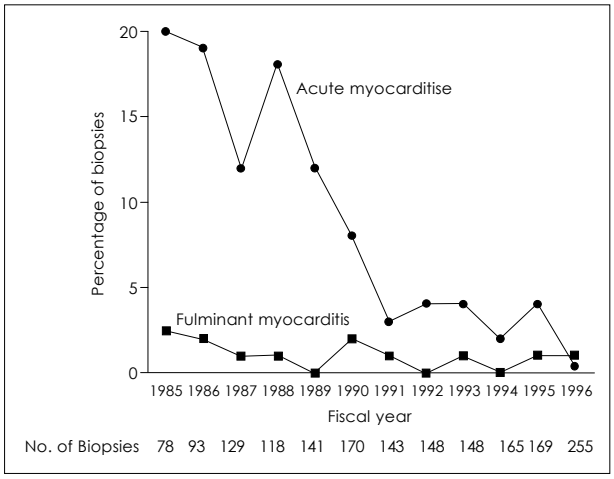

Fig. 2. Cases of acute myocarditis and fulminant myocarditis as a percentage of biopsies performed, 1985 through 1996 (adapted from reference 9).

As described above, FM is defined as a clinicopathological term; moreover, the causative virus of FM has not been well clarified. Therefore, FM can be used, even without identification of the etiologic virus. FM may by caused by an enterovirus, such as coxsackievirus B4, which is associated predominantly with endemic patterns of infection.[29] In mice, coxsackievirus B4 produces a disease similar to fulminant myocarditis.[30] Recently, a few reports clearly identified that FM is associated with coxsackievirus type B (CVB), CVB3 and adenovirus.[17][22][23] Finally, it is possible that FM is not due to viral infection at all, rather, due to an autoimmune disorder,[31] and giant cell myocarditis, which often needs heart transplantation.[32]

Clinical Features

The hemodynamic compromise of fulminant myocarditis develops very rapidly, usually within 1 to 2 day, and leads to ventricular dysfunction, which either resolves spontaneously or results in death. Of the vital signs on admission, approximately 80% of patients have clear consciousness, and half have a SBP less than 90 mmHg. Not all patients are New York Heart Association (NYHA) functional classification IV on admission. Even if the vital signs are stable on admission, a few patients can suddenly develop low cardiac output syndrome or life threatening arrhythmia, so it is necessary to closely observe at the intensive care unit.

The initial and cardinal symptoms are summarized in Table 1. Of the initial symptoms, increased fever, general fatigue and coughing are most common, and of the cardinal symptoms, most are caused by congestive heart failure and low output syndrome. The presence of viral illness should be present within 2 weeks before hospitalization. The average period from initial symptoms to admission is reported 3-5 days.[24] Of the cardinal symptoms, the most frequent are dyspnea, shock, nausea or vomiting, fever, syncope or cramps, chest pain (Table 1, 2) and general fatigue, but these symptoms rapidly develop to severe peripheral circulatory failure, cardiac arrest or life threatening arrhythmia, resulting in the start of MCS within 0.90±1.54 days,[20] or 12 hours.[24]

Table 1. Initial and cardinal symptoms of acute fulminant myocarditis (adapted from reference 20)

Initial symptoms (n=52)		Cardinal symptoms (n=51)	
Increased fever	32 (61.5%)	Dyspnea	20 (39.2%)
General fatigue	12 (23.1%)	Shock	15 (29.4%)
Cough	11 (21.2%)	Nausea/vomiting	11 (21.6%)
Nausea/vomiting	8 (15.4%)	Increased fever	11 (21.6%)
Arthralgia/myalgia	6 (11.5%)	Syncope/cramp	10 (19.6%)
Headache	6 (11.5%)	Chest pain	9 (17.6%)
Chest pain	3 (5.8%)	General fatigue	6 (11.8%)
Syncope/cramp	3 (5.8%)	Abdominal pain	3 (5.9%)
Diarrhea	3 (5.8%)	Diarrhea	2 (3.9%)
Appetite loss	3 (5.8%)	Palpitation	2 (3.9%)
Pharyngalgia	2 (3.8%)	Coughing	1 (2.0%)
Palpitation	2 (3.8%)	Cyanosis	1 (2.0%)
Abdominal pain	1 (1.9%)	Headache	1 (2.0%)
Epigastic pain	1 (1.9%)	Cardiopulmonary arrest	1 (2.0%)
Back pain	1 (1.9%)	Epigastric pain	
Dyspnea	1 (1.9%)	Back pain	1 (2.0%)
Chest discomfort	1 (1.9%)		1 (2.0%)
Common cold	1 (1.9%)		

On the chest X-ray on admission, about 70% of the patients showed congestion of the lungs and slight dilatation of the heart.[20] Also, approximately 80% of patients show either sinus tachycardia or complete atrioventricular block on electrocardiography. Abnormal Q, poor r-progression and low voltage are common findings, in addition to an ST-T abnormality on admission. Ventricular tachycardia may be an initial ECG finding in patients with cardiogenic shock and syncope.[24]

The echocardiographic findings are usually non-specific, slight hypertrophy and pericardial effusion, without dilatation of the left atrium or ventricle. Diffuse or regional hypokinesia, indicating left ventricular (LV) dysfunction, may also be observed. These findings change rapidly, within hours, and progress to circulatory failure in fulminant patients. Therefore, repeated echocardiograms are needed for the early detection of progressive LV systolic dysfunction.[20][24] During the acute phase of myocarditis, transient ventricular (LV) wall thickening can be observed on echocardiograms,[33] because myocardial interstitial edema may occur in the acute phase of myocarditis, resulting in narrowing of the LV lumen and reduction in the stroke volume.[34] Accordingly, LV wall thickening may be predictive of the fulminant course; however LV wall thickening was not significantly different from acute myocarditis.[21] Decreased LVEF on admission was more likely to be associated with a high possibility of developing a fulminant course. Diastolic function has not been investigated in FM patients, but is a worthy subject for future study.[21]

Arterial blood gas analysis, full blood count and biochemical examination revealed that respiratory com-

Table 2. Clinical features and courses of treatment in FM patients in Korea (adapted from reference 24)

No	Age/Sex	Cardinal symptoms	Symptom onset	Machanical circulatory support (MCS)			Etiologic virus
				Time to MCS after admission	MCS type	Applied for	
1	58/F	V-Tac+HF	3 days	6 hours	IABP+LVAD	5 days	CVB4
2	16/M	V-Tac	3 days	Not done	Not done	Not done	CVB 4
3	15/M	AV block+V-Tac	3 days	12 hours	EBS	3 days	CVB 3/4
4	60/F	Chest pain+V-Tac	2 days	6 hours	IABP	14 days	Adenovirus
5	29/F	Chest pain+Shock	2 days	14 hours	EBS	4 days	CVB4
6	40/F	V-Tac	2 days	6 hours	IABP+EBS	12 days	CVB 3
7	32/M	Dyspnea+shock	3 days	3 hours	IABP+EBS	4 days	CVB 3/4
8	41/F	Epigastric pain+shock	5 days	3 hours	IABP+EBS	4 days	CVB 3/4

V-Tac: ventricular tachycardia, HF: heart failure, AV block: atrioventricular block, MCS: mechanical circulatory support, IABP: intra-aortic balloon pump, LVAD: left ventricular assist device, EBS: emergency bypass system with membranous oxygenator, CVB: coxsackievirus type B

pensation for the metabolic acidosis, markedly increased WBC, increased myocardial enzyme levels, renal dysfunction, hyponatremia and increased CRP were common findings. Cardiac troponin T (cTNT) was more useful than creatine kinase (CK), because 60% of patients who had cTNT confirmed on admission showed no significant increases of CK or CK-MB.[20]

For diagnosis of the etiologic virus, the paired serum, 10-14 days apart, should be sampled to test the virus antibody titer. However, the antibody titer changes for CVB were variable, from 28 to 88% in FM patients.[20][24]

It is important to rapidly confirm the diagnosis with coronary angiography and endomyocardial biopsies, without jeopardizing the patient's clinical condition, since FM has an excellent long-term prognosis, so earlier aggressive hemodynamic support is warranted, which results in a better chance of recovery and return to normal life.

Despite an endomyocardial biopsy having been shown to have a low negative predictive value in the diagnosis of myocarditis, it has a high positive predictive value.[35][36] Certainly, endomyocardial biopsy is essential for the definite diagnosis of FM. However, the pathological findings are dependent on the time of the biopsy, from minimal to massive inflammation, with or without fibrosis.[24] Immunohistochemistry, using specific anti-enteroviral antibody, in situ hybridization and reverse transcriptase polymerase chain reaction, using specific viral primers, should be useful methods to identify specific viral protein and genomes (Fig. 3). However, the detection rates are markedly different, which are probably due to differences in the numbers of biopsy samples obtained from each patient.[37-41] Since the mean time to MCS for patients with FM after admission is less than 12 hours, as described above, the inclination would be to begin aggressive treatment if a patient had a clinical picture suggestive of FM, regardless of the histopathological findings. Again, the clinical decision for MCS, rather than the precise diagnosis, is more important for a better chance to save patients with FM. For this reason, even if the vital signs are stable on admission, a few patients can suddenly progress to cardiogenic shock or suddenly develop life threatening arrhythmia, it is necessary to closely observe all such patients with periodic Swan-Ganz catheterization, ECG, echocardiography, full blood count and blood biochemistry, and to prepare life-support systems.

Risk factors of developing FM and Prognostic Factors

The question, "are there serologic biomarkers that will predict the prognosis of patients with fulminant myocarditis?" is a very important, as it has been demonstrated that despite the severity of disease on presentation, a high percentage of patients will survive and completely recover once they overcome the acute phase.[9] Accordingly, it is desirable that the development of the

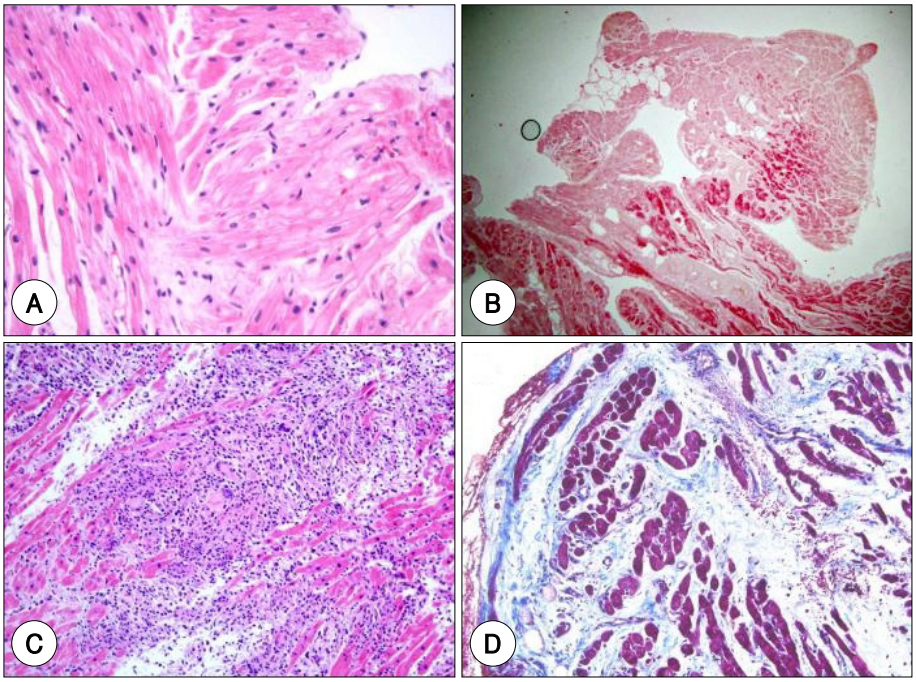

Fig. 3. Pathological findings are dependent on the time of biopsy after the onset of cardinal symptoms of fulminant myocarditis. A: little inflammation was observed in the left atrial specimen, biopsied on day 1 after the onset of symptoms (H & E stain, ×400). B: enteroviral VP1 capsid proteins (red color by alkaline phosphatase) could be detected over the entire biopsied hearts at day 1 (immunohistochemistry, ×200). C: massive myocardial necrosis, inflammation and multinucleated giant cells were identified in the left atrium in a day 5 specimen (H & E, ×100). D: diffuse edema and fibrosis were observed in the day 25 specimen (MT stain, ×200) (adapted from reference 24).

fulminant course in acute myocarditis can be predicted as early as possible, so that the need for MCS can be anticipated. However, there are few reports that have identified the various clinical parameters at the time of admission as indices for predicting the fulminant course and mortality in acute myocarditis.[21-24] Among the parameters at the time of admission, elevated C-reactive protein (CRP), the CK concentrations, decreased LV ejection fraction and intraventricular conduction disturbances increased the risk of a fulminant course in patients with acute myocarditis (Table 3, 4).[21] The patients who require MCS on admission with high mortality, have higher levels of B type natriuretic peptide (BNP) and cTnT, suggesting BNP and cTnT as markers for the severity of HF and myocardial damage, respectively, which might also be useful prognostic markers for fulminant myocarditis.[22-24] Conversely, circulating levels of CRP, a representative marker for the systemic inflammation, and the initial WBC may not be predictive of higher mortality or the fulminant course.[22][24] Other important factors concerning the prognosis were the severity and grade of the cardiac and renal dysfunction, the adjusted support flow rate to enable recovery from circulatory failure, prevention of circulatory disturbances of the legs and multiple organ failure directly associated with MCS.[20]

Table 3. Predictors of fulminant myocarditis based on a logistic regression anaysis (adapted from reference 21)

	Adjusted confidence	Odds ratio interval 95%	p
C-reactive protein	1.41	0.96-2.08	0.08
Creatine kinase	1.00	0.99-1.00	0.78
Intraventricular conduction disturbance	27.38	1.48-507.20	0.03
Left ventricular ejection fraction	0.95	0.87-1.03	0.22

Table 4. Clinical characteristics of patients with acute myocarditis at high and low risk of developing a fulminant course (adapted from reference 21)

	High-risk group (n=13)	Low-risk group (n=20)
C-reactive protein (mg/dl)	6.8±6.6	2.1±2.4
Creatine kinase (IU/L)	1,223.7±830.7	406.4±369.1
Intraventricular conduction	12 (92)	1 (5)
Left ventricular ejection fraction (%)	42.0±12.6	48.9±12.6
Fulminant myocarditis, n (%)	9 (69)	2 (10)

The significance of cytokines in the pathogenic mechanism of human myocarditis remains uncertain. It has been demonstrated in experimental myocarditis that cytokines, such as interleukin (IL)-6, IL-10, IL-12, IL-1α, tumor necrosis factor (TNF)-α and interferon (IFN)-gamma, play a crucial role in the development of myocarditis.[42-49] In addition, some reports have suggested that serum levels of cytokines were elevated in human myocarditis.[50][51] These findings imply that cy-

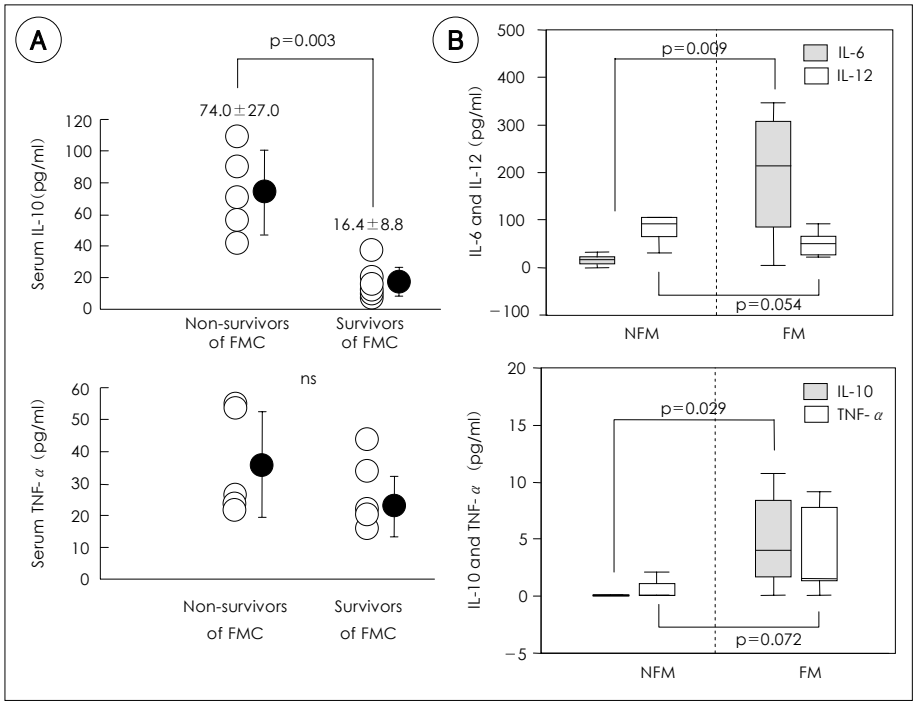

Fig. 4. A: comparison of the serum levels of interleukin (IL)-10 and tumor necrosis factor (TNF)-α on admission between the non-survivors and survivors from fulminant myocarditis. The serum levels of IL-10 on admission, but not those of TNF-alpha, increased considerably in the five non-survivors compared with the nine survivors from fulminant myocarditis with cardiogenic shock that required mechanical circulatory support (adapted from reference 22). B: comparison of the serum levels of interleukin (IL)-6, IL-10, IL-12 and TNF-α on admission between acute coxsackieviral B (CVB) myocarditis and fulminant CVB myocardits (adapted from reference 24).

tokines may be candidates for determining the prognosis in acute myocarditis.

Among the cytokines that may be involved in the pathogenesis of viral myocarditis, the serum IL-10 level on admission has been reported as a discriminating marker in FM. The IL-10 levels could discriminate the patients who would require MCS after admission from those who would not. In addition, those who would ultimately die from their disease had the highest levels of IL-10. Importantly, the average serum IL-10 levels were higher in patients with FM than in those with acute MI who also required MCS, but none of the patients with either fatal or non-fatal MI that required MCS had IL-10 levels as high as those who died of FM. These findings indicate that IL-10 might be a useful prognostic marker in patients with fulminant myocarditis (Fig. 4A).[22] Recently, the IL-6 level on admission has also been reported as a predictor of the fulminant course in CVB acute viral myocarditis (Fig. 4B).[24] IL-10 is generally thought of as an immunosuppressive cytokine, and IL-6 known as a key cytokine in inflammation; however, their exact roles in myocarditis are unclear. Therefore, on the basis of these initial results, a multi-centered study, on a larger population, should be considered to confirm the significance of the serum cytokine levels in patients with both fulminant and non-fulminant myocarditis, including chronic active or persistent myocarditis.

With regard to the long-term prognosis of patients treated for MCS, the readmission, exacerbation, and mortality rates were 10, 3.3 and 10%, respectively, during the average follow-up period of 962 days.[20]

Types of Mechanical Circulatory Support in Fulminant Myocarditis

Devices for circulatory support (CS) are currently used in three broad categories: 1) acute CS with support <1 month; 2) more prolonged support from 30 days to <1 year; and 3) permanent support as an alternative to transplantation. The acute, short-term group includes patients who have cardiac failure after cardiac operations, myocardial infarction (MI) shock or acute cardiomyopathy due to myocarditis or other causes, with a potential likelihood of recovery.[52] FM is characterized by rapid and extensive hemodynamic compromise occurring in a previously healthy patient. However, if the patient survives the acute phase of heart failure, recovery occurs in a few weeks, with a good long-term prognosis.[8-19] Therefore, mechanical circulatory support (MCS), such as IABP, VAD and PCPS, is indicated in FM patients as a 'bridge-to-recovery' as in CS category 1. However, the type of device, technique of implantation and explantation, in addition to weaning protocol, remain unclear.

Extracorporeal membrane oxygenation (ECMO) and VAD are 2 effective advanced mechanical supports suitable for the treatment of FM if IABP is inadequate or infeasible for the initial support. The choice of device is still debatable. In recent literature, the rapid development of VAD, and its successful applications in several patients with myocarditis, either left VAD (LVAD) or biventricular assist devices (BiVAD), has been described.[10-12][17][18][53-55] In the acute form of myocarditis, which may require a long time on device, often as a bridge to transplantation, an implantable LVAD is more appropriate, as long as the right ventricular function is expected to be adequate. On the contrary, in FM, the device is indicated as a bridge-to-recovery, with the time on the device usually being short (mean delay of support was 10 days). So, an extracorporeal device seems logical. BiVAD, in such a diffuse biventricular disease, may be useful. ECMO has many advantages (rapid peripheral technique of insertion), essentially in children.[13-17] However, inadequate unloading of the LV in a child required changing to a BiVAD from ECMO support, due to an efficient unloading of the LV as a condition for rapid recovery should initially be considered.[56] In FM with intractable cardiogenic shock, the use of a BiVAD, as a bridge to recovery, is a life saving approach, which must be considered early before multiend organ failure.[19]

In another opinion, ECMO is preferred to VAD, as the later usually is available in only a few centers, and an implantable VAD is very expensive. Therefore, in most centers, VAD is usually preserved for selected candidates waiting for heart transplantation. Furthermore, the fewer complications, easier application and biventricular support of ECMO, mean ECMO should be considered as the first-line treatment of mechanical support for FM with profound shock when IABP is inadequate or infeasible.[57][58] In my opinion, ECMO is preferred as the MCS in FM, since VAD is still not available, is very expensive and experience is limited in Korea Furthermore, ECMO can be easily applied percutaneously (Table 2).[24]

Guidelines of Mechanical Circulatory Support in Fulminant Myocarditis

Although FM patients have been able to recover and return to normal life, with the help of mechanical cardiopulmonary support, therapeutic guidelines for using MCS for FM have not been established. Recently, the therapeutic guidelines reported by the scientific committee of the Japanese Circulation Society were very informative and unique. A national survey was planned by investigating the current situation of patients with FM requiring MCS and; thereby, formulate therapeutic guidelines for the use of PCPS for this disease; therefore, investigators gathered information on patients

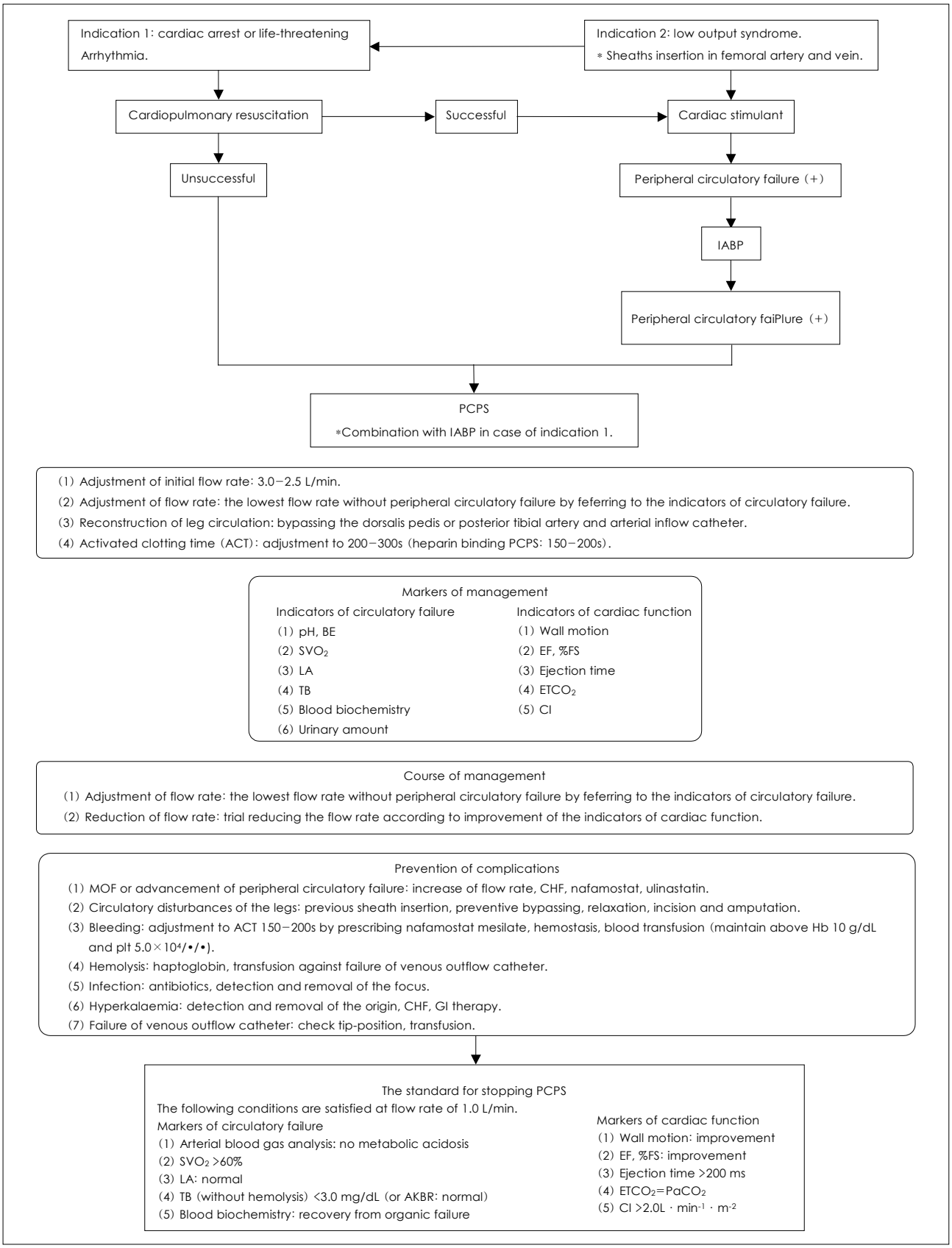

Fig. 5. The guidelines of the PCPS for acute fulminant myocarditis (adapted from reference 20). IABP: intra-aortic balloon pump, PCPS: percutaneous cardiopulmonary support, SVO_2: mixed venous blood oxygen saturation, EF: ejection fraction, LA: left atrium, TB: total bilirubin, $ETCO_2$: end-tidal carbon dioxide partial pressure, CI: cardiac index, MOF: multi-organ failure, CHF: congestive heart failure.

(n=52) with fulminant myocarditis, who were treated with PCPS in Japan over a 3-year period, from April 1997 to March 2000. Finally they proposed guidelines of MCS for acute FM, which are shown in Fig. 5.

Since the mean time to MCS for patients with FM after developing the cardinal symptoms is less than 12 hours, as described earlier,[20)24)] and the hospital mortality of FM is 7-40% with MCS, the inclination would to begin aggressive treatment if a patient had a clinical picture suggestive of FM, rather than wait for the histopathological diagnosis. Again, the clinical decision for MCS is more important than the precise diagnosis, for a better chance to save patients with FM. For this reason, even if the vital signs are stable on admission, a few patients can suddenly progress to cardiogenic shock or suddenly develop life-threatening arrhythmia, it is necessary to closely observe all such patients with periodic Swan-Ganz catheterization, ECG, echocardiography, full blood count and blood biochemistry, and prepare for life-support systems.

Among the clinical parameters obtained at the time of admission, an elevated CRP, CK, cytokine concentrations, decreased LV ejection fraction and intraventricular conduction disturbances, which have been known as prognostic factors.[20-24)] may be helpful in the decision making as to whether the MCS should be applied. It should also be borne in mind that earlier MCS support helps save the life and prevent multi-organ failures of patients with FM. There have been a few case reports suggesting that immunoglobulin and murine OKT3 monoclonal antibody may be effective in the treatment of FM; however, these treatments are not currently recommended.[59)60)] Moreover, the effects of antiviral or immunosuppressive agents[61)] have not been confirmed either.

Conclusion

Although fulminant myocarditis is known as a fatal disease, once patients have recovered, with aggressive pharmacologic therapy and/or MCS, they may return to normal life, with an excellent long-term prognosis. Elevated CRP, CK and cytokine concentrations, and decreased LV ejection fraction and intraventricular conduction disturbances on admission may predict the progress of the fulminant course. Early MCS helps to save the life and prevent multi-organ failures of patients with FM. The type of MCS may not affect the outcome of the clinical course when the complications of MCS are properly managed. Since other managements with immunoglobulin, antiviral agent or monoclonal antibody remain to be confirmed, aggressive hemodynamic support with MCS is the best management for patients with FM, who once recovered from the acute phase, can return to normal life.

REFERENCES

1) Mason JW, O'Connell JB, Herskowitz A, et al. *A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 1995;333:269-75.*
2) Herskowitz A, Campbell S, Deckers J, et al. *Demographic features and prevalence of idiopathic myocarditis in patients undergoing endomyocardial biopsy. Am J Cardiol 1993;71:982-6.*
3) Feldman AM, McNamara D. *Myocarditis. N Engl J Med 2000;343:1388-98.*
4) Dec GW Jr, Palacios IF, Fallon JT, et al. *Active myocarditis in the spectrum of acute dilated cardiomyopathies: clinical features, histologic correlates, and clinical outcome. N Engl J Med 1985;312:885-90.*
5) Lee GH. *Current opinion in viral myocarditis and dilated cardiomyopathy: new paradigms for congestive heart failure. Korean Circ J 2001;31:129-38.*
6) Kawai C. *From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. Circulation 1999;99:1091-100.*
7) Figulla HR. *Transformation of myocarditis and inflammatory cardiomyopathy to idiopathic dilated cardiomyopathy: facts and fiction. Med Microbiol Immnunol 2004;193:61-4.*
8) Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. *Clinicopathologic description of myocarditis. J Am Coll Cardiol 1991;18:1617-26.*
9) McCarthy RE 3rd, Boehmer JP, Huban RH, et al. *Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000;342:690-5.*
10) Rockman HA, Adamson RM, Dembitsky WP, Bonar JW, Jaski BE. *Acute fulminant myocarditis: long-term follow-up after circulatory support with left ventricular assist device. Am Heart J 1991;121:922-6.*
11) Chang AC, Hanley FL, Weindling SN, Wernovsky G, Wessel DL. *Left heart support with a ventricular assist device in an infant with acute myocarditis. Crit Care Med 1992;20:712-5.*
12) Sung BY, Lim BK, Kim YC, et al. *A case of histologically confirmed coxsackiviral myocarditis supported by a left ventricular assist device. Korean Circ J 2000;30:1275-80.*
13) Yasu T, Murata S, Katsuki T, et al. *Acutely severe myocarditis successfully treated by percutaneous cardiopulmonary support applied by a newly developed heparin-binding oxygenator and circuits. Jpn Circ J 1997;61:1037-42.*
14) Kato S, Morimoto S, Hiramitsu S, Nomura M, Ito T, Hishida H. *Use of percutaneous cardiopulmonary support of patients with fulminant myocarditis and cardiogenic shock for improving prognosis. Am J Cardiol 1999;83:623-5.*
15) Inoue Y, Kaneko H, Yoshizawa Y, Morikawa A. *Rescue of a child with fulminant myocarditis using percutaneous cardiopulmonary support. Pediatr Cardiol 2000;21:158-60.*
16) Duncan BW, Bohn DJ, Atz AM, French JW, Laussen PC, Wessel DL. *Mechanical circulatory support for the treatment of children with acute fulminant myocarditis. J Thorac Cardiovasc Surg 2001;122:440-8.*
17) Seong IW, Choe SC, Jeon ES. *Fulminant coxsackieviral myocarditis. N Engl J Med 2001;345:379.*
18) Grinda JM, Chevalier P, D'Atellis N, et al. *Fulminant mycarditis in adults and children: bi-ventricular assist device for recovery. Eur J Cardiothorac Surg 2004;26:1169-73.*
19) Leprince P, Combes A, Pavie A, et al. *Circulatory support for fulminant myocarditis: consideration for implantation, weaning, and explatation. Eur J Cardiothorac Surg 2003;24:399-403.*
20) Aoyama N, Izumi T, Imaizumi T, et al. *National survey of fulminant myocarditis in Japan: therapeutic guideline and long-*

term prognosis of using percutaneous cardiopulmonary support for fulminant myocarditis. Circ J 2002;66:133-44.
21) Kato S, Morimoto S, Hiramitsu S, et al. *Risk factors for patients developing a fulminant course with acute myocarditis. Circ J 2004;68:734-9.*
22) Nishii M, Inomata T, Takehana H, et al. *Serum levels of interleukin-10 on admission as a prognostic predictor of human fulminant myocarditis. J Am Coll Cardiol 2004;44:1292-7.*
23) Knowlton KU, Yajima T. *Interleukin-10: biomarker or pathologic cytokine in fulminant myocarditis? J Am Coll Cardiol 2004;44:1298-300.*
24) Cho DK, Park JI, Park SW, et al. *Predictors of clinical manifestations and courses in patients with acute fulminant coxsackievirus myocarditis. Eur J Heart Failure 2005;4 (Suppl 1):1-104.*
25) *Nonpolio enterovirus surveillance - United States, 1993-1996. MMWR Morb Mortal Wkly Rep 1997;46:748-50.*
26) Kim YJ, Choi RK, Lee MY, et al. *A case of viral myocarditis presenting as acute extensive myocardial infarction. Korean Circ J 1992;22:890-7.*
27) Lee KR, Park TH, Joo CU, Ko JK. *A case of transient complete atrioventricular block in acute viral myocarditis. Korean Circ J 1994;24:335-9.*
28) Kim JH, Jang HJ, Jin DK, Ryu KH, Lee Y. *A case of acute fulminant myocarditis progressed into and recovered from congestive heart failure and multiorgan failure. Korean Circ J 1999;29:316-21.*
29) Pallansch MA. *Epidemiology of group B coxsackieviruses. In: Bendinelli M, Friedman H, editors. Coxsackieviruses: a general update. New York: Plenum Press;1988. p.399-417.*
30) Khatib R, Chason JL, Silberberg BK, Lerner AM. *Age-dependent pathogenicity of group B coxsackieviruses in Swiss-Webster mice: infectivity for myocardium and pancreas. J Infect Dis 1980;141:394-403.*
31) Anandasabapathy S, Frishman WH. *Innovative drug treatments for viral and autoimmune myocarditis. J Clin Pharmacol 1998;38:295-308.*
32) Cooper LT Jr, Berry GJ, Shabeti R. *Idiopathic giant-cell myocarditis: natural history and treatment. N Engl J Med 1997;336:1860-6.*
33) Hauser AM, Gordon S, Cieszkowski J, Timmis GC. *Severe transient left ventricular 'hypertrophy' occurring during acute myocarditis. Chest 1983;83:275-7.*
34) Morimoto S, Kato S, Hiramitsu S, et al. *Narrowing of the left ventricular cavity associated with transient ventricular wall thickening reduces stroke volume in patients with acute myocarditis. Circ J 2003;67:490-4.*
35) Hauck AJ, Kearney DL, Edwards WD. *Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. Mayo Clin Proc 1989;64:1235-45.*
36) Chow LH, Radio SJ, Sears TD, McManus BM. *Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. J Am Coll Cardiol 1989;14:915-20.*
37) Li Y, Bourlet T, Andreoletti L, et al. *Enteroviral capsid protein VP1 is present in myocardial tissues from some patients with myocarditis or dilated cardiomyopathy. Circulaton 2000;101:231-4.*
38) Badorff C, Knowlton KU. *Dystrophin disruption in enterovirus-induced myocarditis and dilated cardiomyopathy: from bench to bedside. Med Microbiol Immunol 2004;193:121-6.*
39) Saji T, Matsuura H, Nakayama T, Hoshida H, Matsuo N. *Detection of enterovirus RNA in fulminant myocarditis by fluorescent in situ hybridization. Circulation 1995;92 (Suppl):787-8.*
40) Bowles NE, Richardson PJ, Olsen EG, Archard LC. *Detection of Coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. Lancet 1986;1:1120-3.*
41) Why HJ, Meany BT, Richardson PJ, et al. *Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy. Circulation 1994;89:2582-9.*
42) Knowlton KU, Badorff C. *The immune system in viral myocarditis: maintaining the balance. Circ Res 1999;85:559-61.*
43) Gluck B, Schmidtke M, Merkle I, Stelzner A, Gemsa D. *Persistent expression of cytokines in the chronic stage of CVB3-induced myocarditis in NMRI mice. J Mol Cell Cardiol 2001;33:1615-26.*
44) Schmidtke M, Gluck B, Merkle I, Hoffmann P, Stelzner A, Gemsa D. *Cytokine profiles in heart, spleen, and thymus during the acute stage of experimental coxsackievirus B3-induced chronic myocarditis. J Med Virol 2000;61:518-26.*
45) Watanabe K, Nakazawa M, Fuse K, et al. *Protection against autoimmune myocarditis by gene transfer of interleukin-10 by electroporation. Circulation 2001;104:1098-100.*
46) Nishio R, Matsumori A, Shioi T, Ishida H, Sasayama S. *Treatment of experimental viral myocarditis with interleukin-10. Circulation 1999;100:1102-8.*
47) Wessely R, Klingel K, Kandolf R, Knowlton KU. *Cardioselective infection with coxsackievirus B3 requires intact type I interferon signaling: implications for mortality and early viral replication. Circulation 2001;103:756-61.*
48) Shioi T, Matsumori A, Nishio R, Ono K, Kakio T, Sasayama S. *Protective role of interleukin-12 in viral myocarditis. J Mol Cell Cardiol 1997;29:2327-34.*
49) Lim BK, Choe SC, Shin JO, et al. *Local expression of interleukin-1 Receptor antagonist by plasmid DNA improves mortality and decreases myocardial inflammation in experimental coxsackieviral myocarditis. Circulation 2002;105:1278-81.*
50) Matsumori A, Yamada T, Suzuki H, Matoba Y, Sasayama S. *Increased circulating cytokines in patients with myocarditis and cardiomyopathy. Br Heart J 1994;72:561-6.*
51) Fuse K, Kodama M, Okura Y, et al. *Predictors of disease course in patients with acute myocarditis. Circulation 2000;102:2829-35.*
52) Stevenson LW, Kormos RL, Bourge RC, et al. *Mechanical Cardiac Support 2000: current applications and future trial design. J Am Coll Cardiol 2001;37:340-70.*
53) Chen JM, Spanier TB, Gonzalez JJ, et al. *Improved survival in patients with acute myocarditis using external pulsatile mechanical ventricular assistance. J Heart Lung Transplant 1999;18:351-7.*
54) Houel R, Vermes E, Tixier DB, et al. *Myocardial recovery after mechanical support for acute myocarditis: is sustained recovery predictable? Ann Thorac Surg 1999;68:2177-80.*
55) Uedo T, Bergin P, Richardson M, Esmore DS. *Bridge to recovery with left ventricular assist device for fulminant acute myocarditis. Ann Thorac Surg 2000;69:284-6.*
56) Ward KE, Tuggle DW, Gessouroun MR, Overholt ED, Mantor PC. *Transseptal decompression of the left heart during ECMO for severe myocarditis. Ann Thorac Surg 1995;59:749-51.*
57) Chen YS, Yu HU, Huang SC, et al. *Experience and result of extracorporeal membrane oxygenation in treating fulminant myocarditis with shock: what mechanical support should be considered first? J Heart Lung Transplant 2005;24:81-7.*
58) Asaumi Y, Yasuda S, Morii I, et al. *Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. Eur Heart J 2005 [Epub ahead of print]*

59) Bilinska ZT, Grzybowski J, Szajewski T, et al. *Active lymphocytic myocarditis treated with murine OKT3 monoclonal antibody in a patient presenting with intractable ventricular tachycardia. Tex Heart Inst J 2002;29:113-7.*
60) Kim HS, Sohn S, Park JY, Seo JW. *Fulminant myocarditis successfully treated with high-dose immunoglobulin. Int J Cardiol 2004;96:485-6.*
61) Jeon ES, Kwak BS, Park KN, et al. *The effects of cyclophosphamide on experimental viral myocarditis. Korean Circ J 1993;23:390-407.*