Table 1 The characteristics of patients with fulminant myocarditis using ECMO (F group)

Age, gender	Time interval to application (h)	Inotropic agents before support	Indication for support	Haemodynamics					Echocardiography				IABP	Pacing	Outcomes
				SBP (mmHg)	HR (b.p.m)	RA (mmHg)	PCW (mmHg)	CI (L/min/m^2)	MR	TR	IVCd (mm)	Pericardial effusion			
67 years, F	20	DA16, DB8, NE0.2, E0.14	Hypotension	80	111	12	24	1.4	−	−	18	+	Y	N	Dead
59 years, M	18	DA6, DB10	Hypotension	94	136	10	16	3.1	−	−	21	+	Y	N	Weaned
22 years, F	12	DA5, DB10	VT/VF	86	120	12	18	1.9	+	−	14	+	Y	N	Weaned
37 years, M	36	DA11, DB6, NE0.3	Hypotension	64	152	17	29	2.7	+	−	29	+	Y	N	Weaned
32 years, F	26	DA3, DB3	VT/VF	76	126	13	16	2.1	+	+	21	+	N	Y	Weaned
53 years, F	26	DA20, DB20	Cardiac arrest	NM	NP						15	+	N	N	Dead
24 years, M	7	DB3	Hypotension	84	122	10	25	1.4	+	−	20	+	N	N	Weaned
29 years, M	14	DA5	VT/VF	60	180	20	25	4.3	−	−	18	+	N	Y	Weaned
16 years, M	11	DA11	Hypotension	80	117	17	21	2.0	−	−	19	+	Y	N	Dead
54 years, F	8	DA3, DB3	VT/VF	90	156	17	28	2.9	+	−	22	+	N	Y	Weaned
49 years, F	15	DB3	Hypotension	60	110	16	19	1.7	+	−	15	+	N	N	Weaned
22 years, F	18	DA27, DB27	Hypotension	53	150	15	25	1.9	−	−	19	+	N	N	Weaned
31 years, M	12	DA10, DB15, NE0.5	Hypotension	88	132	2	21	2.2	++	+	19	+	N	N	Weaned
42 years, M	15	DA5	Hypotension	47	70[a]	15	30	1.4	+	−	17	+	Y	Y	Dead

SBP, systolic blood pressure; HR, heart rate; RA, right atrial pressure; PCW, pulmonary capillary wedge pressure; CI, cardiac index; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; IVCd, inferior vena cava dimension size; DA, dopamine; DB, dobutamine; NE, norepinephrine; E, epinephrine; VT/VF means the existence of ventricular tachycardia or ventricular fibrillation; NM, not measured; NP, not palpable.

[a]Heart rate by temporary right ventricular pacing.

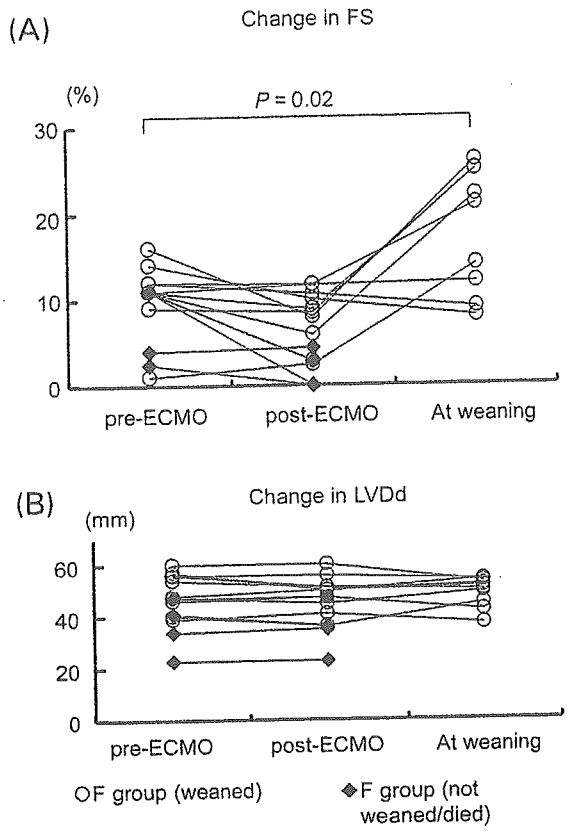

Figure 2 Acute changes in left ventricular function before and immediately after the support and at weaning from ECMO in patients with fulminant myocarditis (F group). (*A*) FS and (*B*) LVDd. Open circles indicate patients who were weaned from ECMO and closed diamonds indicate F patients who were not weaned from ECMO and died.

Discussion

This study demonstrated that ~70% of patients with fulminant myocarditis supported by percutaneous ECMO could be saved. Cardiac function was severely depressed in the acute phase but improved markedly in the chronic phase. The clinical course in the chronic phase in the patients with fulminant myocarditis who were weaned from ECMO was similar to that in patients with non-fulminant myocarditis.

Survival and percutaneous ECMO

McCarthy *et al.*[8] reported that fulminant myocarditis is a distinct clinical entity with an excellent long-term prognosis. However, there were few patients requiring circulatory supports in their reports, and the clinical outcome of those patients remains undetermined. In our series of patients, even though cardiac function was severely depressed in the acute phase reaching zero myocardial FS, haemodynamic volume support by percutaneous ECMO could effectively prevent the development of multiple organ failure. When compared with left ventricular assist devices, which we used to treat 106 patients with deteriorated haemodynamics since 1982, percutaneous ECMO has an advantage in terms of its quick, easy, and less invasive application,[4-6] which may help in overcoming potential complications such as stroke, peripheral arterial ischaemia, haemorrhage, and infections.[16] If there is no improvement in cardiac function, the patients should be bridged from ECMO to ventricular assist devices. The present study includes only one bridged patient. The results derived from other studies of fulminant myocarditis showed a survival rate of 40–50% for patients supported with ventricular assist devices.

Patients with fulminant myocarditis may be better managed by maintaining circulatory support than pursuing transplantation. As reported previously, the survival rate of patients with post-cardiotomy shock who required ECMO but had already suffered from irreversible myocardial damage was 20–40%.[17] However, the present study demonstrated that many of these patients (≈70%) have a reasonable chance for full cardiac recovery and benefit from several days or weeks of circulatory support using ECMO, without undergoing transplantation. Particularly for children in whom transplantation is certainly not encouraging, ECMO is useful in delaying transplantation by providing support sufficiently long to determine whether cardiac function may improve.[18]

Temporary myocardial damage in patients with fulminant myocarditis

In the present study of fulminant myocarditis, patients who were not weaned from ECMO and died exhibited a higher peak CK-MB level and a more depressed systolic function (lower FS) than those who were weaned from ECMO. Interestingly, despite similar peak CK-MB levels, there was a significant difference in FS between patients with fulminant myocarditis who were weaned from ECMO and those with non-fulminant myocarditis. These findings indicate that the extent of myocardial dysfunction and necrosis caused by inflammatory responses may determine the acute outcome in myocarditis patients. Moreover, it is speculated that the echocardiographic finding of less dilatation may be related to a severe infectious insult with myocardial oedema. In light of accumulating evidence, myocardial dysfunction is associated with cardiodepressant mediators including free radicals and inflammatory cytokines.[19,20] From the current data shown in *Figure 2*, percutaneous ECMO does not appear to directly promote functional recovery. However, it may be useful in supporting a compromised heart until the inflammatory storm in the myocardium has subsided. Potential therapies specific for the pathophysiological process of acute myocarditis include immunomodulation (i.e. immunoglobulin and interferon)[21-23] and vaccination,[24,25] the use of which may provide new insights into the treatment of this disease. Duncan *et al.*[7] reported that mechanical circulatory support in combination with immunotherapy (intravenous administration of gamma globulin and/or steroids) results in 60% of the acute survival of children with fulminant myocarditis.

Recovery of ventricular function and long-term outcome

In patients with fulminant myocarditis who survived, FS improved in the chronic phase to a level similar to that in patients with acute non-fulminant myocarditis. The present results were different from those reported previously by Felker *et al.*[26] They reported a significant improvement in FS in patients with fulminant myocarditis (from 19±4 to 30±8%), whereas no improvement was

Table 2 Comparison between patients who were weaned and those who were not weaned from ECMO in the F group

	Patients who were weaned ($n = 10$)	Patients who were not weaned/died ($n = 4$)	P-value
Aspartate aminotransferase (IU/L)	145 (108–381)	280 (208–3775)	0.138
Alanine aminotransferase (IU/L)	70 (54–358)	81 (60–2123)	0.524
Lactate dehydrogenase (IU/L)	635 (475–1229)	1222 (630–6301)	0.358
Peak CPK (IU/L)	3860 (1097–6168)	12005 (7167–16117)	0.138
Peak CK-MB (IU/L)	102 (16–134)	229 (200–538)	0.042
Blood urine nitrogen (mg/dL)	18.5 (15–26)	34.5 (30–38.5)	0.004
Serum creatinine (mg/dL)	1.0 (0.8–1.1)	2.4 (1.55–2.6)	0.179
White blood cell count (/μL)	11635 (9230–12200)	8535 (6400–12885)	0.289
C-reactive protein (mg/dL)	10.2 (6.6–12.4)	7.9 (4.5–15.1)	0.832

The median (25–75%) data. All data except peak creatine phosphokinase (CPK) and its isoform (CK-MB) are presented as baseline (measured on admission).

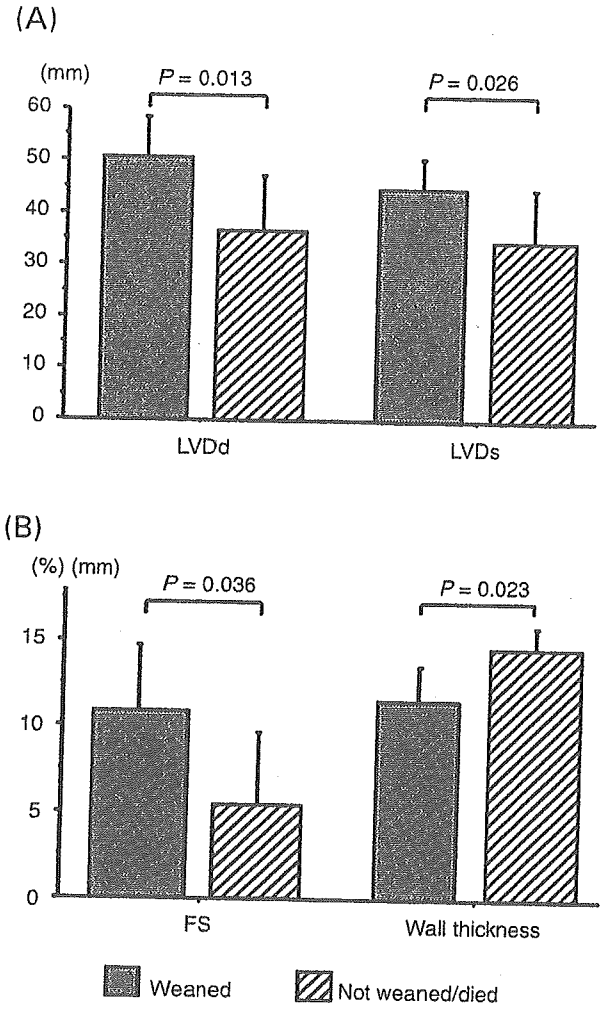

Figure 3 Comparison of echocardiographic data between patients who were weaned and those who were not weaned from ECMO in F group. All these data were gathered on admission. (*A*) LVDd and LVDs. (*B*) FS and ventricular wall thickness.

observed in those with acute myocarditis (from 17±7 to 19 ± 7%). We also noted that the percentages of adverse clinical events were similar between the two groups during the follow-up period. Only one patient in the present study group was rehospitalized due to heart failure.

However, the previous studies showed that the long-term outcome of patients with acute myocarditis was poor, that is, 50–60% of patients had a 5-year survival rate, compared with those with fulminant myocarditis.[8,27,28] This difference may be due to the differences in patients' clinical backgrounds. In the present study, all the 14 patients with fulminant myocarditis and 12 of 13 patients with non-fulminant acute myocarditis had a distinct onset of cardiac symptoms within a short duration from flu-like symptoms and had no recurrence of myocarditis. The myocarditis cases observed in the present study appear to be more acute than those reported by others.[8,28] In the previous studies, designed on the basis of the classification of Lieberman's report,[29] enrolled patients with acute non-fulminant myocarditis had heart failure without a distinct onset of cardiac symptoms, which lasted for a period of weeks to months. The timing of cardiac symptom presentation may be associated with the pathophysiology and/or the state of myocarditis. Patients in the previous studies may have included those with acute myocarditis without distinct onset and/or chronic (active or persistent) myocarditis. Kodama *et al.*[30] showed the long-term favourable outcome of acute myocarditis patients with a distinct onset classified by clinical subtypes, compared with those without a distinct onset. Patients with myocarditis without a distinct onset may have already undergone the remodelling process following a viral infection, leading to dilated cardiomyopathy. Thus, the clinical presentation may play an important role in the prognosis of this particular disease.[31]

Study limitations

This study has a few potential limitations. First, this is a retrospective cohort study performed at one centre. The number of patients was too small to permit multivariate analysis with adjustment for underlying confounders. However, the clinical relevance of the findings regarding such a rare but life threatening disease allows the present comparison. Secondly, endomyocardial biopsy was not performed in all the patients. Endomyocardial biopsy is of value in evaluating the activity of inflammation and identifying infiltrating cells. However, Dec *et al.*[32] demonstrated that the combination of the clinical features of viral myocarditis and subsequent substantial improvement in the left ventricular function suggest the clinical diagnosis of active myocarditis, even when supportive biopsy evidence

Table 3 Comparison with laboratory data between F groups and NF (non-fulminant acute myocarditis) groups

	F group ($n = 14$)	NF group ($n = 13$)	P-value
Aspartate aminotransferase (IU/L)	188 (108–381)	46 (39–127)	0.006
Alanine aminotransferase (IU/L)	70 (57–358)	42 (27–69)	0.051
Lactate dehydrogenase (IU/L)	711 (477–1229)	361 (175–491)	0.004
Peak CPK (IU/L)	3903 (1765–11667)	529 (253–1042)	<0.001
Peak CK-MB (IU/L)	117 (67–210)	98 (67–124)	0.447
Blood urine nitrogen (mg/dL)	24 (16–32)	11 (9–19)	0.003
Serum creatinine (mg/dL)	1.0 (0.8–1.6)	0.75 (0.6–0.85)	0.004
White blood cell count (/μL)	11385 (9049–12200)	9030 (7550-9918)	0.099
C-reactive protein (mg/dL	9.9 (5.4–12.4)	3.6 (2.6-12.3)	0.201

The median (25–75%) data. All data except peak creatine phosphokinase (CK) and its isoform (CK-MB) are presented as baseline (measured on admission).

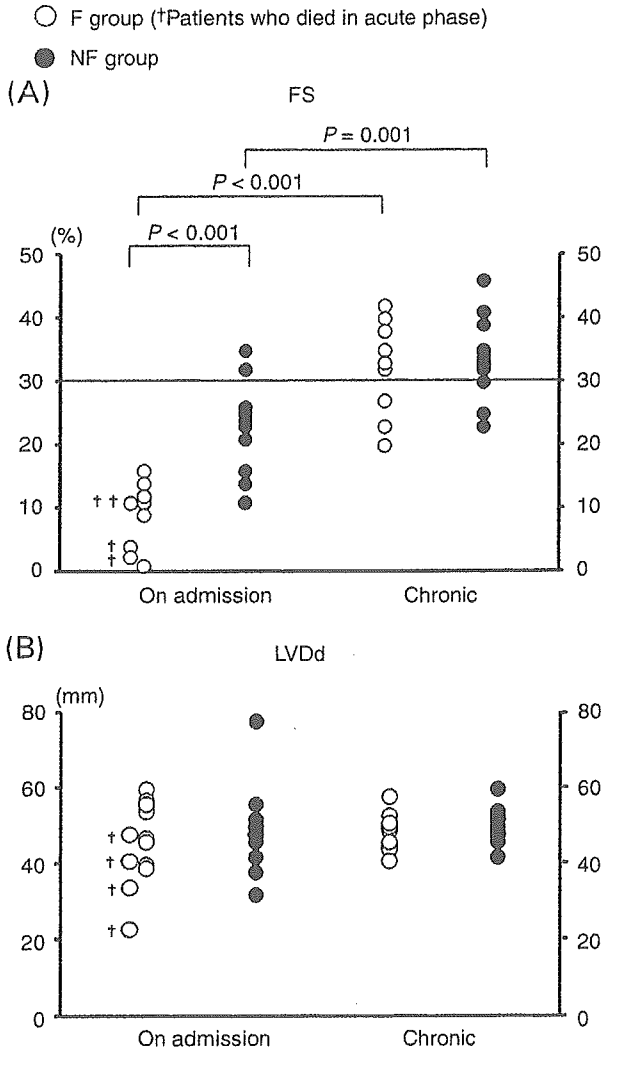

Figure 4 Changes in FS (*A*) and LVDd (*B*) (determined by echocardiography) on admission, in the chronic phase (~6–12 months after). Open circles indicate F group, closed circles indicate non-fulminant acute myocarditis (NF) group, and crosses indicate patients who died.

is lacking. In the present study, as shown in *Figure 4*, left ventricular function recovered to almost normal in the chronic phase and was not accompanied by cardiac dilatation or remodelling. Thus, biopsy was deemed unnecessary;

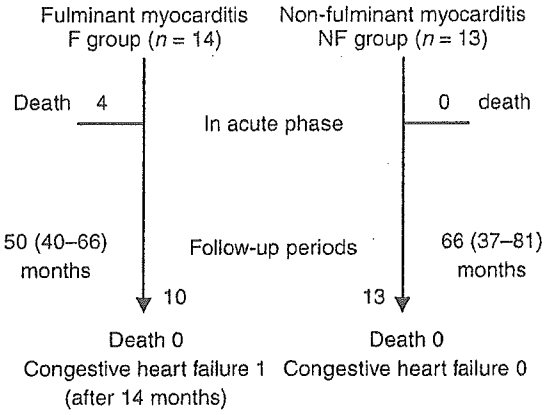

Figure 5 Clinical events in follow-up period.

in some cases, it is difficult to obtain informed consent from the patients of this study.

In conclusion, percutaneous ECMO is a highly effective form of haemodynamic support for patients with fulminant myocarditis. Once a patient recovers from inflammatory myocardial damage, the subsequent clinical outcome is favourable, similar to that observed in patients with acute non-fulminant myocarditis. A further study is required to determine the potential trigger promoting the remodelling process following viral myocarditis.

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ORIGINAL ARTICLE

Ryozo Omoto, MD · Shunei Kyo, MD
Motonobu Nishimura, MD · Hikaru Matsuda, MD
Goro Matsumiya, MD · Soichiro Kitamura, MD
Takeshi Nakatani, MD · Shinichi Takamoto, MD
Minoru Ono, MD · Koichi Tabayashi, MD
Ryohei Yozu, MD

Japanese multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system

Abstract Implantable left ventricular assist device systems (LVAS) are increasingly being used to bridge patients to heart transplantation because of the limited number of available donor hearts. This prospective, multicenter trial was designed to evaluate the usefulness of the HeartMate vented electric (VE) LVAS as a bridge to transplantation in Japan. Between November 2001 and June 2003, six patients with end-stage heart failure [New York Heart Association (NYHA) class IV] were supported with the LVAS and five of the six were able to implement the evaluation (one dropped out). The five were men with an average age of 38.6 years and were supported for 2390 cumulative days (6.6 years). Average preimplant cardiac index improved from 1.93 l/min/m^2 to a 3.79 l/min/m^2 VAD flow index at the end of the clinical trial. All five patients improved to NYHA class I or II, survived more than 1 year, and one patient was discharged from the hospital. Mean LVAS support duration was 478 days (range 390–575 days) and four patients remain supported. One patient died from cardiac failure and sepsis. Device-related complications included: infections (four patients), thromboembolism (one patient), hemolysis (two patients), and repeat operation for bleeding (two patients). There was one case of inflow valve incompetence and two pump motor malfunctions. We conclude that the LVAS can effectively support patients as they await cardiac transplantation and offers improvement to the patient's quality of life.

Key words Implantable left ventricular assist system · Multicenter clinical study · End-stage heart failure · Bridge to transplantation · Patient discharge program

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R. Omoto (✉) · S. Kyo · M. Nishimura
Department of Surgery, Saitama Medical School, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan
Tel. +81-49-276-1562; Fax +81-49-276-2062
e-mail: eikyo501@saitama-med.ac.jp

H. Matsuda · G. Matsumiya
Division of Cardiovascular Surgery, Department of Surgery, Osaka University Graduate School of Medicine, Suita, Japan

S. Kitamura · T. Nakatani
Department of Organ Transplantation, National Cardiovascular Center, Suita, Japan

S. Takamoto · M. Ono
Department of Cardiothoracic Surgery, University of Tokyo, Tokyo, Japan

K. Tabayashi
Department of Thoracic and Cardiovascular Surgery, Tohoku University School of Medicine, Miyagi, Japan

R. Yozu
Department of Cardiovascular Surgery, Keio University Hospital, Tokyo, Japan

Introduction

Implantable left ventricular assist devices (LVADs) have been used worldwide to assist end-stage heart failure patients.[1–3] The HeartMate vented electric (VE) implantable, left ventricular assist system (LVAS) (Thoratec, Pleasanton, CA, USA) is widely used as a bridge to transplantation and recently became the first LVAD to receive Food and Drug Administration (FDA) approval for permanent use in patients with end-stage heart failure ineligible for heart transplantation.[2,3] The recent FDA approval for permanent use was primarily based on the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial that compared the HeartMate VE LVAS and optimal medical therapy for patients with end-stage heart failure who were ineligible for heart transplantation. The trial demonstrated that LVAD therapy provided a clear survival benefit and improved quality of life.[4–8] According to Thoratec's voluntary registry data, more than 3000 HeartMate devices have been implanted worldwide.[9]

In Japan, approximately 152000 people died from heart failure in 2002. Moreover, there are more than 60 patients currently listed on the Japan Organ Transplant Network awaiting a suitable donor heart.[10] Unfortunately, because of

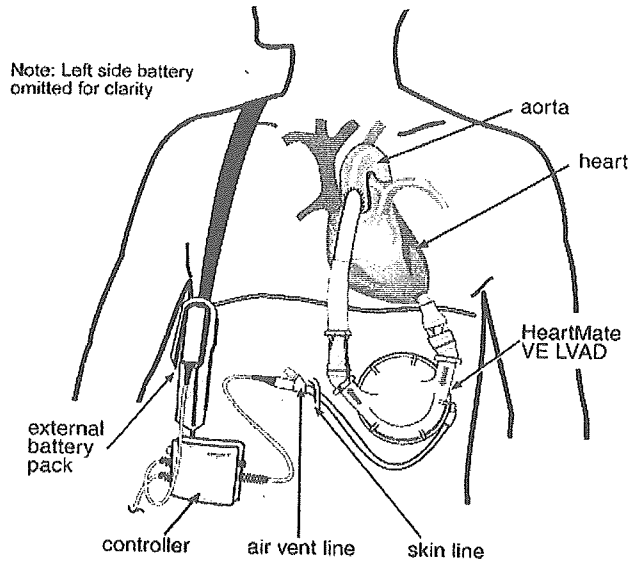

Fig. 1. The HeartMate vented electric (*VE*) left ventricular assist system. The blood pump is situated in the left upper quadrant of the abdomen with a percutaneous lead exiting from the right lateral side. The patient wears a system controller on a belt and a pair of batteries in a shoulder harness

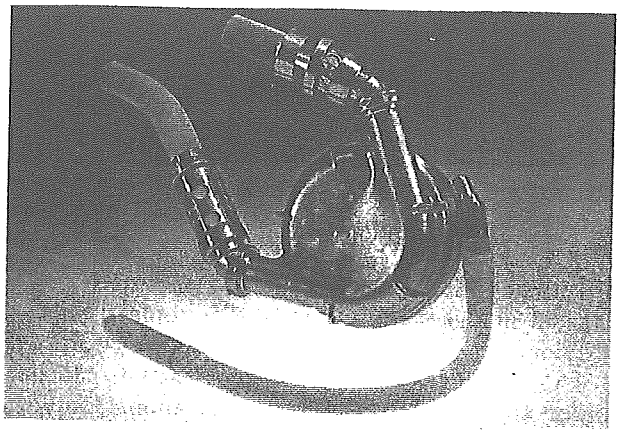

Fig. 2. The HeartMate vented electric left ventricular assist device

the severe donor organ shortage, there were only 17 patients who underwent cardiac transplantation in Japan from 1997 to 2003. Among them, 11 patients required implantable or paracorporeal heart assist devices.[10] Without such devices, most patients would have died prior to transplantation. Although the HeartMate VE LVAS has been widely used around the world, its safety and effectiveness inside and outside the hospital have not been evaluated in Japan. Therefore, we implemented a similar protocol to that used in the United States bridge to transplantation study, used for FDA approval, to demonstrate that the HeartMate VE device also works for Japanese patients.

Materials and methods

Devices

The HeartMate VE LVAS (Fig. 1) is electrically powered and consists of an implanted blood pump, external system controller, and external power supply components. The pump weighs about 1100 g and is approximately 11.2 cm in diameter and 4 cm thick (Fig. 2). The system utilizes a pusher-plate blood pump that is capable of providing a stroke volume of 83 ml and of generating pulsatile blood flow up to 10 l/min. Two pump rate control options are available: auto and fixed rate modes of operation. In the auto mode, the beat rate of the pump is automatically varied as a function of the volume of blood entering the pump chamber to maintain the pump stroke volume at 75 ml per beat. In the fixed rate mode, on the other hand, the physician sets the rate of the pump from 50 to 120 bpm, and the stroke volume depends on filling. The controller calculates the stroke volume by measuring the motor current; the status of the pump, including pump flow (pump rate multiplied by stroke volume), pump rate, and stroke volume are shown on the system monitor.

The pump consists of a rigid titanium housing divided in half by a flexible diaphragm. One half functions as the blood chamber, whereas the other half contains the motor and the actuator that provide the force to move the diaphragm to eject blood from the pump. The blood-contacting surfaces of the pump chamber and its conduits are textured to promote the formation of a biological neointima lining that markedly reduces the thrombogenicity of the device. The textured surface is fabricated from titanium microspheres of 75–100 μm diameter deposited on the titanium housing and conduits. As a result of this surface and the use of tissue valves, an antiplatelet regimen consisting of 81 mg aspirin has been used for most patients.

A percutaneous lead connects the pump to the system controller, which powers the pump and continuously monitors and reports on system function. The vent line is incorporated into the percutaneous lead and serves the dual purpose of venting and pneumatic actuation. A pneumatic driver or emergency handpump can be connected to the externalized vent line and used as an alternative drive system, providing safety backup in the event of failure of the electrical drive system. Power is provided to the system by a pair of wearable, rechargeable batteries that last for 5–8 h depending on the age of the batteries and the pumping conditions. The system includes a bedside power base unit for charging the batteries and providing a direct source of electric power.

Implantation

The pump was implanted in each patient via a median sternotomy incision during cardiopulmonary bypass support. The device was placed in either the intra-abdominal or preperitoneal space. The porcine-valved inflow conduit was inserted in the left ventricular (LV) apex and a woven

Dacron outflow graft was anastomosed to the ascending aorta. Blood flows from the LV through the inflow cannula into the pump and is then ejected into the ascending aorta. As the patient is weaned from cardiopulmonary bypass support, the device is activated.

Participating trial centers

Six leading Japanese cardiovascular surgery centers participated in this study by entering a contract with Nipro Corporation, the exclusive distributor of the HeartMate VE LVAS in Japan. The six centers (listed in alphabetical order) are Keio University Hospital, National Cardiovascular Center, Osaka University Hospital, Saitama Medical School Hospital, Tohoku University Hospital, and Tokyo University Hospital. This study was carried out under the Good Clinical Practice Guidelines. Informed consent was obtained prior to study participation and each study site obtained its own institutional review board approval prior to study initiation.

Study design

The US FDA approved the safety and effectiveness of the HeartMate VE LVAS as a bridge to cardiac transplantation in 1998. This Japanese trial also investigates the safety and effectiveness of the HeartMate device for use inside and outside the hospital using a similar protocol to that the US study. However, patients in this study were excluded from evaluation if they required support with another circulatory support device after HeartMate LVAS implantation.

The Japanese study was a multicenter, prospective clinical trial conducted according to a common protocol. All subjects were monitored for VAD flow and adverse events, including any deaths, device malfunctions, or failures, throughout the duration of the study. The study interval was 1 year and all patients were followed to transplantation or for 1 year, whichever occurred first. This trial required that patients remain hospitalized for the first 6 months (phase I) and then patients were eligible for discharge from the hospital (phase II). Prior to hospital discharge, the patient and at least one companion were required to learn device operation and appropriate emergency responses for the HeartMate LVAS. Once proficiency was demonstrated, the patient was allowed to take three excursions daily and then at least three overnight stays away from the hospital. The investigator would then determine if the patient could safely be discharged to an outpatient residence within 1-h access to the hospital.

Patient selection

Trial entry criteria included patients eligible for cardiac transplantation and listed on the Japan Organ Transplant Network. Eligible patients were older than 15 years with a body surface area greater than or equal to 1.5 m^2 and of New York Heart Association (NYHA) functional class IV with no response to maximal pharmacological treatment such as digitalis, diuretics, angiotensin-converting-enzyme inhibitors, nitrates, or beta-blockers. Moreover, the inclusion criteria included at least one of the following: (1) systolic pressure less than 80 mmHg or a cardiac index less than 2.0 l/min/m^2 with pulmonary capillary wedge pressure greater than 20 mmHg; (2) dependence on catecholamines, such as dobutamine, dopamine, epinephrine, norepinephrine, and/or PDE III inhibitor, or (3) dependence either on intra-aortic balloon pumping, percutaneous cardiopulmonary support, and/or Japanese domestic left ventricular assist device. The exclusion criteria for this trial are shown in Table 1.

Table 1. Exclusion criteria for the VE LVAS clinical trial in Japan

Exclusion criteria
1. Severe infection.
2. Irreversible multiple organ failure
3. Pregnancy
4. Severe chronic obstructive pulmonary disease
5. Pulmonary embolism within 30 days
6. Severe pulmonary hypertension
7. Cardiac operation within 2 weeks
8. Severe hepatic diseases
9. Severe central nervous disturbances
10. Nontreatable abdominal aneurysm
11. Severe peripheral vascular diseases
12. Malignant diseases, such as sever bleeding, chronic renal dysfunction, and/or cancer
13. Significant obesity
14. Alcohol or drug addiction
15. Psychoneurotic disorder history and unable to follow or impossible to understand the protocol
16. Any other contraindications to cardiac transplantation

VE LVAS, vented electric left ventricular assist system

Data acquired

To observe the effectiveness of the HeartMate VE LVAS, pump parameters were recorded daily for the first 30 days and then monthly. Patient clinical parameters including NYHA classification were evaluated at the same time intervals. Hemodynamic parameters such as cardiac output, pulmonary artery wedge pressure (PCWP), central venous pressure (CVP), and pulmonary arterial pressure (PAP) were recorded daily until extubation. In addition, blood gases were measured daily until extubation.

Blood analysis [white blood cell count, red cell count, platelet count, hematocrit, hemoglobin, creatinine, blood urea nitrogen (BUN), glutamic oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), total bilirubin, partial thromboplastin time (PTT), prothrombin time (PT), and plasma free hemoglobin] were measured to monitor end-organ function and hemolysis as per the adverse event definitions as specified below. All abnormal lab. values were reviewed to determine if they met any adverse event definitions.

Table 2. Patient baseline demographics

Patient number	Sex	Diagnosis	Age (years)	BSA (m^2)	Blood pressure (mmHg) systole/diastole	Cardiac index ($l/min/m^2$)	Left ventricular end-diastolic diameter (mm)	NYHA class
1	Male	DCM	30	1.50	85/55	1.6	80	IV
2	Male	DCM, MR	21	1.61	78/64	1.7	72	IV
3	Male	DCM	48	1.56	78/56	1.9	84	IV
4	Male	DCM	44	1.70	96/64	2.4	78	IV
5	Male	DCM	50	1.77	80/34	2.03	72	IV
Mean±SD			38.6 ± 12.6	1.63 ± 0.11	83.4 ± 7.6/54.6 ± 12.3	1.93 ± 0.31	77.2 ± 5.2	IV

DCM, dilated cardiomyopathy; MR, mitral valve regurgitation; BSA, body surface area; SD, standard deviation; NYHA, New York Heart Association

Table 3. Support duration and outcome for each patient (as of June 2003)

Patient number	Support duration (days)			Outcome[a]
	Electric	Pneumatic	Total	
1	397	178	575	Ongoing
2	390	–	390	Explanted and died
3	550	–	550	Ongoing
4	445	–	445	Ongoing
5	388	42	430	Ongoing
Mean ± SD	434.0 ± 68.9	110.0 ± 96.2	478.0 ± 80.2	–

[a]At the end of Phase II study (12 months)

Adverse events

Safety was evaluated by collecting data for all adverse events that occurred while patients were enrolled in the study. Adverse events were collected for both in-hospital and out-of-hospital LVAS use and included device malfunctions and failures. This paper describes only those adverse events considered to be device-related. Infections were considered to be device related when no infection was identified preoperatively. Bleeding from the connection sites or from the prosthetic graft of the HeartMate VE LVAS was considered a device-related adverse event. In addition, all thromboembolism was considered to be device related. Any hemolysis after 3 days of device implantation was considered a device-related adverse event. Furthermore, device malfunction was defined as any instance in which any component of the system failed to perform in the intended manner. Finally, device failure was defined as the inability of the VE LVAS, including its backup components, to maintain life support in the patient.

Statistical analysis

Statistical analysis was performed by the STATA software package (Stata Corporation, College Station, TX, USA). All data is expressed as mean ± SD. The changes before and after LVAS implantation were evaluated by paired *t* test.

Results

Baseline characteristics

A total of six patients were enrolled from November 2001 to June 2003. One patient required a right ventricular assist device in addition to the HeartMate VE LVAS, and could not be weaned from the device. This patient died 25 days after implantation as a result of multiple organ failure and was excluded from further analysis. The remaining five patients were men ranging in age from 21 to 50 years with an average body surface area of 1.63 ± 0.11 m^2. All patients were diagnosed with dilated cardiomyopathy and had compromised hemodynamics with dependence on intravenous inotropes (Table 2). Two of the five patients had multiple organ failure (one had renal and respiratory failures and the other had hepatic and respiratory failures), and two additional patients had had hepatic failure prior to VAD implantation.

Effectiveness of the LVAS support

All five patients survived for more than 1 year and were supported for 2390 cumulative days (6.6 years). Mean LVAS support duration was 478 days (range 390–575 days) and four patients remained on LVAS support as of June 2003 (Table 3). One patient died from cardiac failure and sepsis after LVAS removal on postoperative day 390;

Table 4. Hematological data

	Baseline	Final value	*P* value[a]
Hemoglobin (g/dl)	12.3 ± 3.2	11.0 ± 2.2	0.4478
Hematocrit (%)	36.2 ± 9.0	34.6 ± 6.4	0.7302
WBC (10^3/mm^3)	7.8 ± 1.2	9.0 ± 3.4	0.4447
Platelet count (10^3/mm^3)	214 ± 137	207 ± 58	0.9112
APTT (sec)	84.9 ± 86.7	43.7 ± 7.3	0.3188
PFHb (mg/dl)	9.6 ± 10.5	10.8 ± 6.9	0.8043

Data are expressed by mean ± SD
Final value is that at the end of phase II study
WBC, white blood cell; APTT, activated partial thromboplastin time; PFHb, plasma free hemoglobin
[a] Paired *t* test

Table 5. Hepatic and renal function data

	Baseline	Final value	*P* value[a]
Total bilirubin (mg/dl)	1.76 ± 0.87	0.74 ± 0.35	0.0844
GOT (IU/l)	22.6 ± 10.6	24.8 ± 12.3	0.7724
GPT (IU/l)	16.6 ± 7.2	13.4 ± 5.7	0.3977
BUN (mg/dl)	20.6 ± 7.8	21.6 ± 18.3	0.9162
Creatinine (mg/dl)	0.94 ± 0.30	1.02 ± 0.23	0.6038

Data are expressed by mean ± SD
Final value is that at the end of phase II study
GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BUN, blood urea nitrogen
[a] Paired *t* test

Table 6. Summary of device malfunctions observed in the clinical study

Malfunctions	Patients	Events	Days of support prior to malfunction (days)
External components			
Power base unit and cable	2	2	136–376
System controller	3	5	154–375
System monitor	1	1	0
Battery	2	3	61–69
Y-connector	2	5	133–468
Stroke volume limiter	2	5	23–168
Internal components			
Pump motor	2	2	388–399
Inflow valve	1	1	178
Total	–	24	–

removal was necessitated by a fungal infection on the pump's outflow graft that resulted in a cerebral infarction.

The average pump index for each subject was greater than 2.0 l/min/m^2 throughout the study. The pump index was consistently greater than 2.0 l/min/m^2 in four of the five patients. One patient initially experienced dehydration related to poor appetite, which decreased the total circulating volume and resulted in a cardiac index of less than 2.0 l/min/m^2. Once this patient regained their appetite, the pump index increased to more than 2.0 l/min/m^2. The average pump index (3.79 ± 0.79 l/min/m^2) at the end of the study was approximately twice the preimplant cardiac index (1.93 ± 0.31 l/min/m^2) ($P = 0.0043$). Therefore, the pump was judged to be effective in sustaining circulatory support.

Major hematological values stabilized after device implantation and this supported device effectiveness (Table 4). In addition, renal and hepatic values either stabilized or improved after LVAS implantation (Table 5). Only two patients experienced transient hemolysis postoperatively.

All five patients demonstrated improvement to NYHA class I or II from a baseline NHYA class of IV. One patient was discharged from the hospital after 376 days of LVAS support. However, a device malfunction occurred 12 days after discharge and the patient was readmitted without any adverse effects and was supported pneumatically using a backup driver.

Safety of the LVAS system

A total of 24 device malfunctions were observed in the five patients, of which 21 were related to external components and 3 were related to implantable components (Table 6). One of the three malfunctions of implantable system components was inflow valve incompetence as a result of leaflet deterioration, a torn valve cusp, or both and the other two were motor malfunctions.

In the Phase I study (the first 6 months after implantation), four patients experienced minor external device malfunctions that included a power base unit, system controller, system monitor, Y-connector, and battery, but they were completely resolved by replacing the component. The more serious device malfunction was related to inflow valve regurgitation, which led to development of severe cardiac failure. Therefore, the inflow valve conduit was changed and the cardiac failure disappeared immediately.

In the Phase II study, there were three cases of device malfunction. One patient experienced a motor malfunction 397 days after implantation but was successfully supported with a pneumatic driver. Additionally, motor trouble occurred 388 days after pump implantation in other patient and a pneumatic driver was used as a backup. Approximately 3 weeks after commencement of pneumatic support, the stroke volume limiter (SVL), a driver component, broke, resulting in a thromboembolism episode. The

patient experienced left hemiplegia; however, patient activity was improved dramatically by rehabilitation. In another patient, a fungus infection located in the outflow graft of the device resulted in cerebral infarction. The device was removed on postoperative day 390 and the patient ultimately died of cardiac failure and sepsis.

Overall, there were eight cases of infection in four patients after device implantation: five driveline, one systemic, and two wound infections. A total of seven repeat operations after device implantation were reported. Five of the seven were a result of bleeding immediately after LVAS implantation. Repeat operation was required in one patient to change the inflow valve conduit as a result of inflow valve regurgitation 203 days after LVAS implantation. Another pump was explanted because a fungus infection was observed in the outflow graft.

Discussion

Left ventricular assist devices have dramatically altered the treatment strategy for heart failure patients awaiting heart transplantation.[11] Our primary study purpose was to demonstrate the usefulness of the HeartMate VE LVAS as a bridge to cardiac transplantation. However, during this study, no LVAS patient underwent heart transplantation because of the severe donor shortage in Japan. Therefore, all patients were supported by the LVAS for more than 1 year. Frazier and associates reported that the mean support duration in the US bridge to transplantation study was 105.5 days.[12] In addition, the randomized REMATCH study, which assessed the utility of the LVAS as a permanent form of circulatory support, reported a median LVAS duration of 408 days.[4] As of December 2003, 17 patients had undergone heart transplantation in Japan, of which 11 required mechanical assistance for a mean support duration of 428 days before heart transplantation.[10] Furthermore, the mean support duration reported at the conclusion of this study was 478 days (one died, four ongoing). Considering the current low availability of transplant organs, however, it can be anticipated that the required support duration might be much longer. The device would thus substantially be used like a destination therapy, but the primary purpose of this device is for application as a bridge to transplantation in Japan. The support durations obtained from our experience make the HeartMate device suitable as a bridge to transplantation. In the near future, we consider it necessary to investigate the usefulness of the device as a destination therapy, taking account of the patient's indication.

In this study, we implanted the HeartMate device in six patients, of whom two had a body surface area of $1.5\,m^2$. One patient dropped out of the study. Compared to some other nationalities, Japanese patients, especially women and the elderly, tend to be small, and concerns about the anatomical fitting of the device have been raised. Fortunately, the implantation procedure was successfully completed even in those patients with a body surface area of only $1.5\,m^2$. The implantation criteria regarding body size, a minimum body surface area of $1.5\,m^2$, was set to the same value as in the US, and if patients were smaller than the minimum size, regardless of sex or age, we would apply an extracorporeal LVAD.

The HeartMate VE LVAS also demonstrated effectiveness in stabilizing hemodynamics and maintaining end-organ function with an average pump index for each patient of greater than $2.0\,l/min/m^2$. All renal and hepatic parameters were consistently maintained within normal limits for the LVAS-supported period and thus our experience indicated that LVAD placement is mandatory to preserve end-organ function and to avoid worsening renal and hepatic function induced by severe cardiac failure.

Infectious complications were difficult to compare with the literature because no uniformity for reporting these data exists. Reported infection rates range from approximately 20% to 75%, although not all the infections were device related.[13–15] Four (80%) of the five patients in this study had device-related infections. These data indicate that the incidence of device-related infection was relatively high, and infection control and management during LVAS support was not easy. However, the VE LVAS has undergone modification to include a smaller more flexible driveline and a stabilization belt to secure the driveline. These improvements, along with better timing of device implantation, might help to decrease infection rates in the future.[16,17]

There were no thromboembolic complications during electrical LVAS support with use of only antiplatelet agents. However, one patient who switched to pneumatic support experienced a thromboembolic complication as a result of device malfunction related to the SVL. Consequently, a more durable SVL has been developed and introduced.

Other device malfunctions occurring in this study included one case of inflow valve incompetence. Subsequent design modifications have been made to the HeartMate VE LVAS to enhance device reliability and durability. A new inflow valve assembly designed to reduce valve failures and other modifications were recently approved by the FDA and introduced to the market. In addition, Poirier recommends that to avoid inflow valve stress, care must be taken to maintain low arterial pressure.[18] We believe that the incidence of valve regurgitation should decrease as a result of careful patient managements and the new inflow valve.

Fortunately, device malfunctions in this study were not associated with catastrophic outcomes. Others have also demonstrated that device failures could typically be compensated for or resolved through component replacement with a satisfactory degree of success.[19] We consider that a patient education program focused on system operation training and emergency response procedures is extremely important in Japan. One patient discharged from the hospital faced a device malfunction and successfully returned to the hospital because of adequate training. Furthermore, although device malfunctions may occur, the targeted patients for this device are suffering from advanced end-stage heart failure. Therefore, the benefits associated with this device are considered to be far greater than the potential risks.

Despite these complications, all patients demonstrated improvement in functional capacity to NYHA I or II during LVAS support. Therefore, the LVAS produced a significant improvement in functional capacity and the quality of these patients' lives. In our study protocol, hospital discharge was prohibited for the first 6 months despite fairly good physical and mental conditions in all subjects. It is generally believed that patients supported with LVADs can be discharged between 18 and 77 days postimplantation.[20] Thus, once patients in Japan are no longer restricted by study protocols, they can be discharged from the hospital after recovery from LVAS implantation, providing additional quality of life benefits.

The HeartMate and Novacor implantable LVASs have some advantages compared with extracorporeal LVADs such as high flow rate and untethered operation. Untethered operation is a most important factor given the current transplantation situation in Japan, because the anxiety of awaiting a suitable donor heart can be severe for patients and their families. By returning to a relatively normal lifestyle during cardiac support, patients have a greatly reduced level of anxiety, stress, and depression. In fact, the patient discharged during this study has recovered a good mental state, as mentioned above. In contrast, because patients with extracorporeal LVADs cannot leave the hospital, it is difficult to improve their mental state.

Efficacy was demonstrated by our study in which the device provided adequate hemodynamic support and improved the NYHA functional class of the patients for periods of more than 1 year despite the minor device malfunctions observed. However, further studies are needed in Japan to assess the safety and effectiveness of this device with a larger patient population.

Conclusions

The mean duration of LVAS support in our study was longer than that for the US REMATCH study or the average duration of LVAS support of 11 patients in Japan prior to undergoing cardiac transplantation. Furthermore, considering the improvement of patient quality of life and the severe donor organ shortage, we believe that the HeartMate VE LVAS is an effective therapy for end-stage heart failure patients in Japan as well as worldwide.

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Sex Differences in Early Mortality of Patients Undergoing Primary Stenting for Acute Myocardial Infarction

Masami Kosuge, MD; Kazuo Kimura, MD; Sunao Kojima, MD*; Tomohiro Sakamoto, MD*; Masaharu Ishihara, MD**; Yujiro Asada, MD†; Chuwa Tei, MD††; Shunichi Miyazaki, MD‡; Masahiro Sonoda, MD‡‡; Kazufumi Tsuchihashi, MD§; Masakazu Yamagishi, MD‡; Yoshihiko Ikeda, MD§§; Mutsunori Shirai, MD***; Hisatoyo Hiraoka, MD†††; Takeshi Inoue, MD‡‡‡; Fumio Saito, MD§§§; Hisao Ogawa, MD*; on behalf of the Japanese Acute Coronary Syndrome Study (JACSS) Investigators

Background Limited information exists regarding the impact of gender on in-hospital outcome after primary stenting for acute myocardial infarction (AMI).

Methods and Results A total of 2,981 patients (790 women and 2,191 men) participated in the study who were admitted within 24 h after symptom onset and underwent emergency primary stenting for AMI. Compared with men, women were significantly older; had higher incidences of hypertension, diabetes mellitus, hyperlipidemia, Killip class ≥2, and cardiogenic shock; had a higher blood glucose level and a lower serum creatinine level on admission. Other baseline characteristics, including the incidences of ST-segment elevation AMI, anterior infarction, 3-vessel disease, initial or final Thrombolysis in Myocardial Infarction (TIMI) flow grade did not significantly differ between the sexes. The in-hospital mortality rate was significantly higher in women than in men (9.4% vs 5.2%, p<0.001). On multivariate analysis, age, Killip class, blood glucose level, serum creatinine level, and final TIMI grade were independent predictors of in-hospital death, but female gender was not (odds ratio 1.01, p=0.69).

Conclusions Our findings suggest that in patients undergoing primary stenting for AMI, women have higher in-hospital mortality than men, but female gender itself is not independently associated with increased in-hospital mortality after adjustment for baseline differences. (*Circ J* 2006; **70:** 217–221)

Key Words: Myocardial infarction; Stents; Survial; Women

A number of studies have addressed sex-related differences in outcomes in patients with acute myocardial infarction (AMI). A few studies have reported similar or lower mortality rates after AMI in women than in men[1–4] but most have concluded that mortality is higher in women irrespective of reperfusion modality[5–12] The reasons for poorer outcomes in women remain unclear. Increased mortality in women might be partially explained by their higher age at presentation and higher risk profiles. Some[5–8] but not all[9–12] studies have shown that female gender itself is independently associated with increased mortality after adjustment for baseline differences. One potential explanation for the persistence of increased mortality after risk adjustment is that women frequently receive less aggressive treatment for AMI than men[7,13,14] Primary balloon angioplasty, compared with thrombolytic therapy, has been shown to improve outcomes for women, but mortality remains high[2,10] Limited information exists regarding the impact of sex on outcomes after contemporary interventional techniques, such as stent implantation, for AMI. We therefore analyzed a database from a large, retrospective, multicenter observational study of patients with AMI who underwent emergency primary stenting to assess the outcomes of women compared with those of men.

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*Division of Cardiology, Yokohama City University Medical Center, Yokohama, *Department of Cardiovascular Medicine, Kumamoto University School of Medicine, Kumamoto, **Department of Cardiology, Hiroshima City Hospital, Hiroshima, †First Department of Pathology, Miyazaki University Medical School, Miyazaki, ††The First Department of Internal Medicine, Kagoshima University Faculty of Medicine, Kagoshima, ‡Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, ‡‡The Second Department of Cardiology, National Hospital Kyusyu Cardiovascular Center, Kagoshima, §Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, §§Department of Pathology, National Cardiovascular Center, Suita, ***Department of Microbiology, School of Medicine, Yamaguchi University, Ube, †††Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Suita, ‡‡‡Division of Cardiology, Oita National Hospital, Oita and §§§Department of Cardiology, Nihon University Surugadai Hospital, Tokyo, Japan*

Mailing address: Kazuo Kimura, MD, The Division of Cardiology, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan. E-mail: c-kimura@urahp.yokohama-cu.ac.jp

Methods

Patients

The patients included in the current study were selected from those enrolled into the Japan Acute Coronary Syndrome Study[15] a retrospective, observational multicenter trial. Between January 2001 and December 2003, patients who were admitted to 35 participating hospitals in Japan within 48 h after the onset of AMI were studied. A diagnosis of AMI required at least 2 of the following characteristics: typical chest pain persisting for 30 min or longer,

Table 1 Baseline Characteristics

	Women (n=790)	Men (n=2,191)	p value
Age (years)	73±10	65±11	<0.001
Body surface area (m^2)	1.47±0.14	1.71±0.16	<0.001
Time from symptom onset to admission (h)	4.9±5.0	4.5±5.0	0.09
Killip ≥2 on admission	173 (22%)	331 (15%)	<0.001
Cardiogenic shock on admission	68 (9%)	142 (7%)	0.045
Previous infarction	78 (10%)	245 (11%)	0.31
Previous angina	308 (39%)	799 (37%)	0.21
Diabetes mellitus	273 (35%)	672 (31%)	0.044
Hyperlipidemia	293 (37%)	716 (33%)	0.025
Hypertension	506 (64%)	1,136 (52%)	<0.001
Smoking	131 (17%)	1,248 (57%)	<0.001
Blood glucose level on admission (mmol/L)	10.7±5.1	9.8±4.2	<0.001
Serum creatinine on admission (mg/dl)	0.8±0.7	1.0±0.9	<0.001
ST-segment elevation	688 (87%)	1,930 (88%)	0.46
Peak creatine kinase (IU/L)	2,829±2,676	3,418±3,387	<0.001

Data are presented as mean values±SD or percentages of patients.

Table 2 Angiographic Findings

	Women (n=790)	Men (n=2,191)	p value
Number of diseased vessels			0.97
1	445 (57%)	1,246 (57%)	
2	240 (30%)	657 (30%)	
3	105 (13%)	288 (13%)	
Infarct-related artery			0.29
LAD	384 (49%)	1,024 (47%)	
RCA	283 (36%)	840 (38%)	
LCX	107 (13%)	287 (13%)	
LMT	16 (2%)	33 (2%)	
Bypass graft	0	7 (0.3%)	
TIMI flow grade 0 at initial CAG	512 (65%)	1,456 (67%)	0.40
Final TIMI flow grade ≥2	758 (96%)	2,090 (95%)	0.51
Final TIMI flow grade 3	714 (90%)	1,967 (87%)	0.63

Data are presented percentages of patients.
LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; TIMI, Thrombolysis in Myocardial Infarction.

ischemic electrocardiographic changes, and a peak creatine kinase level equivalent to more than twice the upper limit of normal. A total of 4,432 patients fulfilled the following criteria: 1 admission within 24 h after the onset of AMI; 2 coronary angiography performed immediately after admission; and 3 availability of a detailed clinical history. Reperfusion therapy was performed in 3,635 patients (82%). Of these 3,635 patients, we studied 2,981 (82%) who underwent stenting of the infarct-related artery. The study protocol was reviewed and approved by the ethical committee of each participating hospital.

Definitions

Diabetes mellitus was defined as a fasting glucose concentration of ≥7.0 mmol/L, a blood glucose concentration of ≥11.0 mmol/L on a 75-g, 2-h oral glucose tolerance test, or the use of anti-diabetic treatment. Hypertension was defined as a history of a systolic blood pressure of ≥140 mmHg, a diastolic pressure of ≥90 mmHg, or the use of anti-hypertensive treatment. Hyperlipidemia was defined as a fasting total cholesterol concentration of ≥220 mg/dl, a fasting triglyceride concentration of ≥150 mg/dl, or the use of anti-hyperlipidemic treatment. Preinfarction angina was defined as the presence of typical chest pain occurring at rest or during exercise and persisting for less than 30 min, within 24 h before the onset of AMI.

Coronary Angiography and Coronary Intervention

Coronary angiography was performed immediately after admission. The perfusion status of the infarct-related artery was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) study classification.[6] The recanalization method was left to the physicians' discretion. Stenting was done in all patients in whom the procedure was feasible. Final TIMI flow grade was assessed on the basis of the final angiograms obtained at admission.

Statistical Analysis

Data are expressed as means±SD. Patients with and those without preinfarction angina were compared by using unpaired t-tests. Differences in prevalence were assessed by chi-square tests. A probability value of <0.05 was considered to indicate a statistically significant difference. Multiple logistic regression analysis was used to examine determinants of in-hospital mortality. Analyzed variables included age, sex, hypertension, diabetes mellitus, prior infarction, preinfarction angina, body surface area, time to admission, Killip class, infarct location, blood glucose level and serum creatinine level on admission, occlusion status at the culprit lesion, number of diseased vessels, and final TIMI flow grade. Odds ratios and 95% confidence intervals were calculated. Data were analyzed with the use of SPSS software (Release 10, SPSS, Chicago, IL, USA).

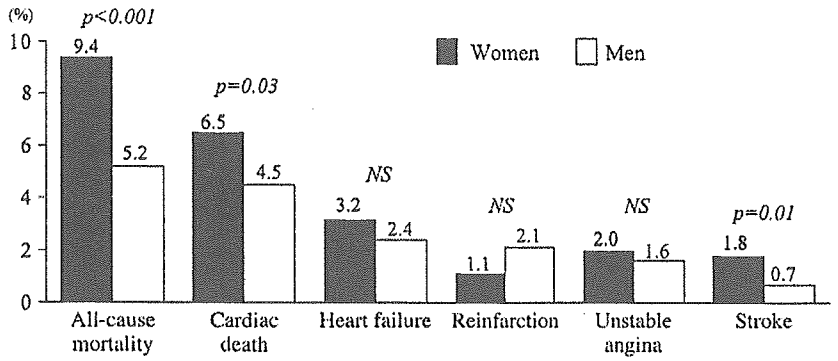

Fig 1. Overall, in-hospital mortality was significantly higher in women (black bars) than in men (white bars). The rates of cardiac death and stroke were also significantly higher in women than in men.

Results

Baseline Characteristics

Of the 2,981 subjects, 2,191 (73%) were men and 790 (27%) were women. The baseline characteristics of the subjects are presented according to sex in Table 1. Women were more likely to be elderly and had a lower body surface area; higher incidences of hyperlipidemia, diabetes mellitus, hypertension, Killip class ≥2, and cardiogenic shock; and a lower frequency of smoking. There was a trend toward a longer time from symptom onset to admission in women, but the difference with men did not reach statistical difference. The frequency of previous infarction, preinfarction angina, and ST-segment elevation did not differ between the sexes. On admission the blood glucose level was significantly higher and the peak creatine kinase level and serum creatinine level were significantly lower in women than in men.

Angiographic Findings

Angiographic findings of the patients are shown in Table 2. There were no significant differences between women and men in the number or distribution of diseased coronary vessels, including 3-vessel disease and left main coronary disease. The initial and final TIMI flow grades did not differ between the sexes.

In-Hospital Outcomes

Clinical outcomes in hospital are shown in Fig 1. In-hospital mortality was significantly higher in women than men. Of the patients who died in the hospital (74 women and 115 men), 51 women and 98 men died of cardiac causes. Women had a higher rate of stroke. Multivariate analysis showed that age, Killip class, blood glucose level or serum creatinine level on admission, and final TIMI grade were independent predictors of in-hospital death, whereas female gender was not (Table 3). Multivariate analysis according to sex showed that age, Killip class, blood glucose level or serum creatinine level on admission,

Table 3 Multivariate Analysis of Factors Associated With In-Hospital Mortality in All Patients

Variable	*Odds ratio (95%CI)*	*p value*
Age	*1.08 (1.04–1.12)*	*<0.001*
Female	*1.01 (0.47–2.04)*	*0.69*
Hypertension	*1.09 (0.42–1.29)*	*0.29*
Diabetes mellitus	*1.04 (0.54–2.02)*	*0.40*
Prior infarction	*1.81 (0.92–3.56)*	*0.09*
Absence of preinfarction angina	*1.55 (0.87–2.76)*	*0.14*
Body surface area	*0.68 (0.43–1.06)*	*0.09*
Time to admission	*1.03 (0.98–1.09)*	*0.23*
Killip class ≥2	*6.43 (3.67–11.3)*	*<0.001*
Anterior infarction	*1.56 (0.89–2.71)*	*0.11*
Blood glucose level on admission	*1.01 (1.01–1.30)*	*0.049*
Serum creatinine level on admission	*1.45 (1.24–1.69)*	*<0.001*
TIMI flow grade 0 at initial CAG	*1.21 (0.68–2.16)*	*0.51*
Multivessel disease	*1.31 (0.74–2.33)*	*0.30*
Final TIMI flow grade	*0.60 (0.41–0.85)*	*0.005*

CI, confidence interval; CAG, coronary angiography; TIMI, Thrombolysis in Myocardial Infarction.

Table 4 Multivariate Analysis of Factors Associated With In-Hospital Mortality According to Sex

Variable	*Women*		*Men*	
	Odds ratio (95%CI)	*p*	*Odds ratio (95%CI)*	*p*
Age	*1.11 (1.03–1.19)*	*0.004*	*1.07 (1.03–1.11)*	*0.001*
Hypertension	*1.09 (0.39–3.03)*	*0.86*	*0.62 (0.31–1.26)*	*0.19*
Diabetes mellitus	*1.03 (0.30–2.91)*	*0.91*	*1.10 (0.47–2.58)*	*0.82*
Prior infarction	*0.95 (0.22–4.19)*	*0.95*	*2.33 (1.06–5.16)*	*0.036*
Absence of preinfarction angina	*1.51 (0.24–1.83)*	*0.42*	*1.52 (0.74–3.17)*	*0.26*
Body surface area	*0.80 (0.06–13.3)*	*0.59*	*0.19 (0.01–2.50)*	*0.21*
Time to admission	*1.08 (1.01–1.17)*	*0.037*	*0.99 (0.91–1.07)*	*0.76*
Killip class ≥2	*5.90 (2.24–15.6)*	*<0.001*	*6.60 (3.24–13.4)*	*<0.001*
Anterior infarction	*1.74 (0.64–4.76)*	*0.28*	*1.68 (0.83–3.38)*	*0.15*
Blood glucose level on admission	*1.17 (1.01–20.6)*	*0.038*	*1.20 (1.05–23.7)*	*0.046*
Serum creatinine level on admission	*1.59 (1.15–11.3)*	*0.005*	*1.42 (1.17–1.71)*	*<0.001*
TIMI flow grade 0 at initial CAG	*0.95 (0.36–2.53)*	*0.91*	*1.36 (0.64–2.86)*	*0.42*
Multivessel disease	*1.05 (0.41–2.65)*	*0.94*	*1.51 (0.72–3.20)*	*0.28*
Final TIMI flow grade	*0.46 (0.23–0.90)*	*0.024*	*0.62 (0.40–0.97)*	*0.037*

CI, confidence interval; CAG, coronary angiography; TIMI, Thrombolysis in Myocardial Infarction.

and final TIMI grade were independent predictors of in-hospital death in both women and men (Table 4).

Discussion

The present study showed that in patients undergoing primary stenting for AMI, women had a higher rate of in-hospital mortality than men did. However, multivariate analysis showed that female gender itself was not an independent predictor of in-hospital mortality.

Similar to previous studies[1-11] women were older than men by 8 years on average and had a lower body surface area, a higher Killip class, and higher incidences of hypertension, diabetes mellitus, and hyperlipidemia. On coronary angiography, the extent of underlying coronary atherosclerosis, evaluated on the basis of the number of diseased vessels, did not differ between women and men, consistent with the findings of previous investigations[2,5,10,12] The current study also found that baseline and post-procedural TIMI flow grades were similar in women and men. Several studies have similarly shown that the TIMI flow grade before and after primary angioplasty for AMI did not differ between women and men[2,10,17] In contrast, Lansky et al found that baseline and post-procedural TIMI grade 3 flows were better in women than in men[11]

Mortality was higher in women than in men, consistent with the results of most previous studies[5-12] This poorer outcome in women was most likely related to the facts that women were older than men, had higher incidences of coronary risk factors such as hyperlipidemia, diabetes mellitus, and hypertension, as well as higher incidences of Killip class ≥2, and cardiogenic shock. These and other factors such as a higher blood glucose level on admission might have negatively affected outcome. Several studies have shown that woman have poorer outcomes than men;[9-11,14] however, after adjustment for other baseline characteristics, female sex itself was not an independent risk factor for increased mortality. Those studies therefore concluded that a higher age or more adverse risk profiles in women contributed to the poorer outcomes. However, several studies reported that female gender itself was an independent predictor of increased mortality, even after adjusting for other baseline characteristics[5-8] These inconsistent results suggest that methodological, as well as biologic factors, must be considered when interpreting the impact of gender on survival after AMI.

Women have been reported to be significantly less likely to receive thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting[6,7,13] The less frequent use of reperfusion therapy in women might be related to their higher mortality. Furthermore, randomized studies have shown that percutaneous coronary interventions are more effective reperfusion strategies than intravenous thrombolysis[18] In the GUSTO II-B PTCA substudy, Tamis-Holland et al suggested that women derived a larger absolute benefit from primary PTCA than from thrombolytic therapy as compared with men[10] Stone et al reported that primary PTCA reduced the risk of intracranial bleeding and improved survival in women enrolled in the PAMI trial[2] In the present study, all patients underwent primary stenting, thereby eliminating possible differences in mortality caused by treatment bias.

Recent studies have investigated the influence of sex on outcome in patients receiving primary coronary intervention for AMI, but whether female gender itself is an independent predictor of increased mortality after AMI remains controversial. Vakili et al reported that after correcting for age and baseline risk differences, women undergoing primary coronary intervention for a first AMI have a higher in-hospital mortality rate than men[5] Lansky et al have shown that female gender is not an independent determinant of death at 1 year and attributed the higher mortality rate in women after interventional treatment for AMI to differences in body size and clinical risk factors[11] Mehilli et al showed that women with AMI who received percutaneous coronary intervention have outcomes similar to those of men, despite more adverse risk profiles[3] Differences in study design, entry criteria, and length of follow-up make it difficult to compare results in different studies. The present study included high-risk patients who are usually excluded from clinical trials, such as those who are elderly and have shock, as well as a high proportion of patients with diabetes mellitus (31%). In addition, we included the blood glucose level and serum creatinine level on admission in our risk analysis. These factors have been shown to be associated with an increased risk of death after AMI[8,19-22] but were not always included in risk analysis in previous studies assessing the impact of sex on outcomes after AMI.

Study Limitations

Several important limitations need to be considered when interpreting our results. First, this was a retrospective, observational, non-randomized study. However, our database was relatively large and included patients treated at hospitals of various sizes and settings, making it more representative of current practice patterns than previous single-site databases or randomized trials. Second, our data did not include information on treatment with aspirin, statin, β-blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists or on the door-to-balloon time, all factors shown to influence mortality from AMI. Furthermore, angiographic data such as the number of stenosed lesions, lesion length, and reference diameter were not obtained. However, in the current study, body surface area, a surrogate for coronary vessel size, was lower in women than in men. Another limitation was that cardiac and non-cardiac causes of death were not fully examined. Further investigations are necessary to determine why women with AMI are more likely to have poorer outcomes compared with men. In addition, prospective studies are needed to verify the effects of gender on clinical outcomes after primary stenting for AMI.

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Determinants of rapid progression of aortic root dilatation and complications in Marfan syndrome☆

Aleksandar M. Lazarevic[a], Satoshi Nakatani[a,*], Yutaka Okita[b], Jelena Marinkovic[c], Yutaka Takeda[a], Keiji Hirooka[a], Hiroshi Matsuo[a], Soichiro Kitamura[b], Masakazu Yamagishi[a], Kunio Miyatake[a]

[a]*Department of Cardiology, National Cardiovascular Center, Suita, Osaka, Japan*
[b]*Department of Cardiothoracic Surgery, National Cardiovascular Center, Suita, Osaka, Japan*
[c]*Cardiovascular Research Center, Dedinje Cardiovascular Institute, Belgrade University Medical School, Belgrade, Serbia and Montenegro*

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Abstract

Background: Progressive aortic dilatation has prognostic significance in the Marfan syndrome.
Methods: To identify which patients were at high risk of rapid progression, we echocardiographically studied 43 patients (age 22 ± 14 years) with the mean follow-up period of 5.2 ± 3.2 years. Aortic diameters, left ventricular (LV) size, fractional shortening, and the severity of aortic and mitral regurgitation were assessed. Transmitral peak early and atrial flow velocities, their ratio and the deceleration time of peak early velocity were also obtained.
Results: Mean annual increases of aortic diameters were 0.4 ± 0.3 mm at the annulus, 1.5 ± 1.3 mm at the sinuses of Valsalva, 0.7 ± 0.6 mm at the supraaortic ridge and 0.4 ± 0.4 mm at the proximal ascending aorta. Patients were divided into 2 groups according to the aortic growth rate at the sinuses of Valsalva level: rapid (R, >3% per year, 15 patients) or slow (S, ≤3% per year, 28 patients) progression groups. Measured variables did not show significant differences between the 2 groups except older age, higher blood pressure and more severe aortic regurgitation in group R. Multiple regression analysis identified prolonged deceleration time as the most important variable predicting aortic complications. Aortic dissection occurred more frequently in group R (7 patients, 47%) than in group S (0%, P<0.001).
Conclusions: Marfan patients at older age, with higher blood pressure, and with significant aortic regurgitation were at high risk of progression of aortic dilatation, with the most remarkable increase at the sinuses of Valsalva. Prolonged deceleration time may relate to an increased risk for aortic complications.

Keywords: Marfan syndrome; Echocardiography; Aortic dissection; LV function

1. Introduction

One of the most serious clinical manifestations of the Marfan syndrome is progressive aortic root dilatation which may lead to aortic dissection, rupture or regurgitation that are responsible for decreased life expectancy in these patients [1–4]. Although aortic root dilatation is observed in 60–80% of Marfan patients [5–7], aortic growth rate among individuals may vary [8] and factors predicting the rate of change of the aortic diameter are still not completely

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* Corresponding author. Department of Cardiology National Cardiovascular Center 5-7-1 Fujishiro-dai, Suita Osaka 565-8565, Japan. Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.
E-mail address: nakatas@hsp.ncvc.go.jp (S. Nakatani).

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Table 2
Echocardiographic variables

	Total ($n=43$)		Group S ($n=28$)		Group R ($n=15$)	
	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up
Aortic sinus diameter (mm)	36.8 ± 8.7	43.2 ± 11.5	33.7 ± 7.2	39 ± 7	42.7 ± 8.4*	51 ± 14†
Aortic sinus ratio	1.36 ± 0.23	1.49 ± 0.32	1.30 ± 0.20	1.37 ± 0.2	1.48 ± 0.24‡	1.72 ± 0.4†
LV EDD (mm)	48 ± 7	52 ± 8	47 ± 8	51 ± 8	50 ± 5	54 ± 9
LV EDDI (mm/m^2)	32 ± 8	32 ± 6	33 ± 9	31 ± 6	31 ± 6	33 ± 7
LV ESD (mm)	31 ± 5	34 ± 7	30 ± 6	33 ± 6	32 ± 4	35 ± 8
LV ESDI (mm/m^2)	21 ± 5	21 ± 5	21 ± 6	20 ± 4	20 ± 5	22 ± 6
FS (%)	36 ± 4	34 ± 5	36 ± 4	34 ± 5	36 ± 5	34 ± 5
IVS (mm)	8.1 ± 1.8	8.6 ± 1.6	7.6 ± 1.6	8.3 ± 1.5	9.0 ± 1.7‡	9.2 ± 1.7
PW (mm)	7.7 ± 1.7	8.3 ± 1.5	7.3 ± 1.5	7.9 ± 1.4	8.5 ± 1.8§	8.9 ± 1.6‖
Aortic regurgitation						
Prevalence	16 (37%)	22 (51%)	5 (18%)	8 (29%)	11 (73%)*	14 (93%)†
Severity	0.5 ± 0.8	0.9 ± 1.2	0.3 ± 0.8	0.4 ± 0.9	0.9 ± 0.7§	1.9 ± 1.1†
Mitral regurgitation						
Prevalence	12 (28%)	19 (44%)	6 (21%)	11 (39%)	6 (40%)	8 (53%)
Severity	0.4 ± 0.7	0.8 ± 1.1	0.2 ± 0.5	0.6 ± 1.0	0.7 ± 1.0	1.0 ± 1.2

*$P=0.001$; †$P<0.001$; ‡$P=0.01$; §$P=0.02$; ‖$P=0.04$ compared with group S. Data presented are mean value ± SD or number (%) of patients. EDD=end-diastolic diameter; EDDI=end-diastolic diameter index, ESD=end-systolic diameter; FS=fractional shortening; IVS=diastolic interventricular septum thickness; PW=diastolic LV posterior wall thickness.

regurgitation (0.7 ± 0.5 vs. 0.5 ± 1.0) and mitral regurgitation (0.7 ± 1.0 vs. 0.2 ± 0.5) between the 2 groups. However, patients in group R showed longer deceleration time ($P=0.005$), lower E ($P=0.015$) and lower E/A ($P=0.002$) compared to those in group S. A wave velocity did not differ significantly between the 2 groups. Follow-up data were available in 17 patients. At the most recent follow-up, deceleration time was longer in group R ($P=0.03$). Other Doppler indexes were comparable between the 2 groups.

3.4. Possible predictors of rapid progression of aortic root dilatation

To identify possible predictors of rapid aortic root dilatation, we performed multiple regression analyses. Aortic root dilatation at the sinuses of Valsalva level and that at the supraaortic ridge level were determined by diastolic pressure (t value=2.091, $P=0.043$ for the sinus level, t value=2.348, $P=0.024$ for the supraaortic ridge level). Changes of aortic ratios at the sinus and supraaortic ridge levels were influenced by diastolic pressure and aortic regurgitation (t value=2.340, $P=0.024$ and t value=2.163, $P=0.037$ for the aortic sinus, and t value=3.374, $P=0.002$ and t value=3.438, $P=0.002$ for the supraaortic ridge). Fig. 3 shows t values of each parameter to predict aortic growth rate with overall multiple correlation coefficient.

Multivariate logistic regression analysis was used to identify the best predictor of rapid aortic dilatation (group R patients). In this analysis, the parameters which differed significantly between groups R and S at initial evaluation were included. They were aortic sinus diameter, aortic sinus ratio, systolic and diastolic blood pressures, degree of aortic regurgitation, deceleration time, E and E/A. The only independent predictor of rapid dilatation was E/A ratio ($P=0.0223$). We also assessed the independent predictors of aortic complications using the logistic regression with the same parameters. The only independent predictor of aortic complications was deceleration time ($P=0.0295$).

4. Discussion

4.1. Features of the patients with rapid progression of the aortic root dilatation

The present study showed that the Marfan patients at older age, with higher blood pressure, and with significant aortic regurgitation were at high risk of rapid progression of

Table 3
Doppler left ventricular diastolic filling variables

	Total		Group S		Group R	
	Initial ($n=27$)	Follow-up ($n=17$)	Initial ($n=15$)	Follow-up ($n=8$)	Initial ($n=12$)	Follow-up ($n=9$)
DT	184 ± 26	196 ± 40	172 ± 15	175 ± 22	199 ± 30*	216 ± 43†
E	62 ± 15	57 ± 14	68 ± 13	63 ± 13	54 ± 14‡	51 ± 14
A	44 ± 13	44 ± 9	40 ± 14	42 ± 10	48 ± 12	46 ± 8
E/A	1.55 ± 0.58	1.35 ± 0.45	1.84 ± 0.57	1.55 ± 0.36	1.19 ± 0.35§	1.18 ± 0.46

*$P=0.005$; †$P=0.03$; ‡$P=0.015$; §$P=0.002$ compared with group S. Data presented are mean value ± SD or number of patients. A=atrial diastolic filling velocity; DT=deceleration time of the early diastolic filling velocity; E=early diastolic filling velocity.

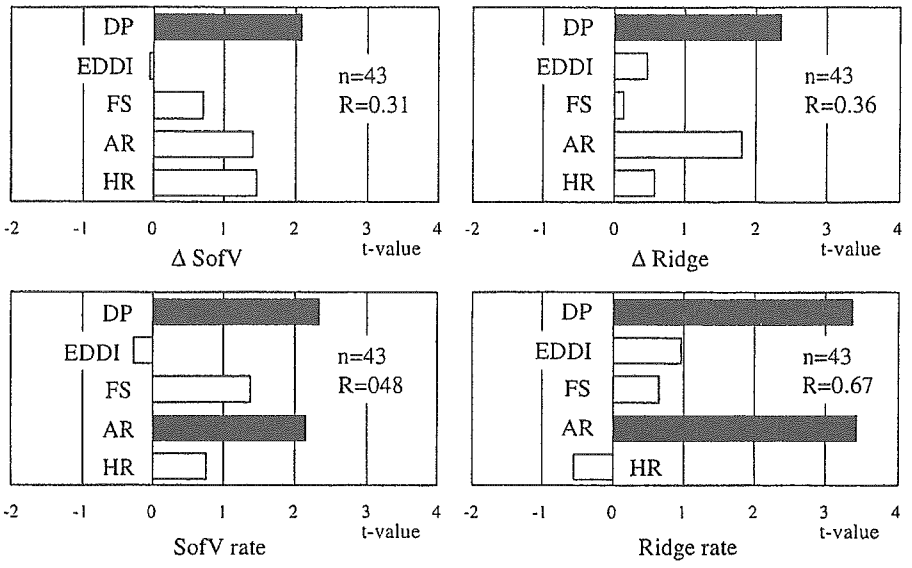

Fig. 3. Impact of patients' characteristics on annual change of aortic root diameter and on change of the aortic ratio; *t* values of each parameter are shown in bar graphs. Black bars indicate $P<0.05$ and white bars indicate $P>0.05$. R shows multiple correlation coefficient. AR=severity of aortic regurgitation; DP=diastolic blood pressure; EDDI=end-diastolic diameter index; FS=left ventricular fractional shortening; HR=heart rate; Δ ridge=change in supraaortic ridge diameter per year; ridge rate=change in supraaortic ridge ratio; Δ SofV=change in aortic sinuses of Valsalva diameter per year; SofV rate=change in aortic sinus ratio.

aortic root dilatation and subsequent aortic complications. Despite significant initial differences between groups in the prevalence and severity of aortic regurgitation, we found that LV size and systolic function were comparable between groups with rapid and slow progression. However, interestingly, abnormal LV diastolic filling pattern, indicating impaired LV relaxation, was more common in patients with rapid progression. Note that in this analysis, factors influencing Doppler filling parameters such as age, blood pressure, LV size, wall thickness, and aortic and mitral regurgitation grades were all comparable between patients with slow and rapid progression. Although there was a relatively small number of patients who had pulsed Doppler recordings, the features associated with impaired diastolic LV relaxation could predict more rapid aortic root dilatation and development of complications in select Marfan patients. Further, our findings could have a logical explanation when considering the potential abnormalities of the collagen matrix that may involve the myocardium in the Marfan syndrome [10]. The abnormalities of the extracellular connective tissue matrix in patients with the Marfan syndrome could involve heart muscle as well as aorta and heart valves, leading to ventricular diastolic dysfunction [10]. It has been speculated that defective microfibrils and elastic fibers in the cardiac cytoskeleton weaken the elastic restoring forces in the Marfan syndrome, and therefore LV relaxation is impaired [10].

4.2. Determinants of rapid aortic root dilatation

Since the Marfan patients with aortic root dilatation may have poor prognosis, it would be clinically important to predict which patients would progressively develop aortic root dilatation. Therefore, we performed multivariate analysis considering clinical and echocardiographic parameters as independent variables and changes in aortic root diameters as the dependent variables. We found that aortic regurgitation grade, diastolic blood pressure and LV size had significant influence on the rate of aortic root dilatation. This finding is in accord with the previously published study regarding the poorer prognosis (decreased long-term survival) in patients with diastolic murmur or cardiomegaly on initial physical examination [4]. The presence of aortic regurgitation or dilated LV, or both should be a sign to proceed in an aggressive manner to further treatment.

4.3. Clinical implications

Our study confirms the importance of age, high blood pressure, larger initial aortic ratio, and presence and severity of aortic regurgitation, abnormal Doppler diastolic filling pattern at baseline as markers of high risk of rapid progression of aortic dilatation and subsequent aortic complications. This underscores the need for more frequent control and aggressive treatment in the Marfan patients with these features.

Diastolic dysfunction has been known to precede systolic dysfunction in some forms of heart failure. We found that even in patients with rapid progression of aortic dilatation (which could represent more severe disease expression) systolic function was preserved. It appears that in the Marfan syndrome, diastolic dysfunction precedes systolic dysfunction. It may be possible that our findings, indicating impaired relaxation, may show an overture to rapid progression of aortic dilatation and the risk for aortic complications in select Marfan patients.