

Fig. 1. 心筋梗塞症における主な使用薬剤の比較

327名(35.2%), 3剤168名(18%)であった。両期間とも2剤併用が最も多く次が単剤であった。1996年ではCa拮抗薬と硝酸薬との併用率が296名(約36%)であり圧倒的に高かったが、2004年では92名(9.9%)と減少した。2004年では単剤投与では、硝酸薬が有意に減少しβ遮断薬が有意に増加したのが特徴的であった。2剤併用では1996年に比較して単剤の使用が多く、2剤併用が減少していた(Fig. 2)。

### 3. Ca拮抗薬の薬剤別の使用頻度について

Ca拮抗薬の薬剤別使用頻度をFig. 3に示した。1996年では、ニフェジピンが241名(46.5%)ともっとも多く、次いでジルチアゼム193名(34.0%)、アムロジピン31名(8.7%)、その他29名(6.6%)の順であった。一方2004年では、アムロジピンの使用頻度が179名(37.1%)ともっとも高く、次いでニフェジピン145名(30%)、ジルチアゼム129名(26.7%)、その他30名(6.2%)の順であった。Ca拮抗薬は血中半減期の長い第3世代に分類されるアムロジピンの使用頻度が高くなり、1996年の約4倍の使用頻度であった。ニフェジピンについては血中濃度半減期が短い速効性は使用されず、第2世代(徐放性製剤)が145名(30%)と多く使用されていた。

### 4. β遮断薬の各薬剤の使用頻度について

当センターのβ遮断薬をβ<sub>1</sub>選択性・内因性交感神経刺激作用(ISA)の有無により、1群から5群にまで分類して調査を行った(Table 2)。心筋梗塞症の患者において1996年では3群106名(63.5%)と使用頻度が最も高く、次に1群30名(18%)、2群15名(9%)、5群12名(7.2%)、4群4名(2.4%)の順であった。2004年では、3群が379名(72.1%)と1996年同様もっとも高い使用頻度であり、次に5群75名(26.4%)の順となり、その他の群に関しての使用頻度は低かった。1996年ではβ<sub>1</sub>非選択性薬剤も投与されていたが、2004年ではβ<sub>1</sub>選択性薬剤ISA(-)とαβ遮断薬に集約されていた。また、αβ遮断薬が約3倍以上の使用頻度の増加を認めた(Table 2)。

3群の使用薬剤については、メトプロロールは1996年62名(58%)が2004年208名(55%)と使用患者数は増加しているが、β遮断薬のうちの使用割合は両年とも同様の結果であり、今回も約半数の患者に処方されていた。5群のうち1996年は5名(41%)であったが、2004年では72名(98%)の患者がカルベジロールの投与を受けていた。

## 考 察

心筋梗塞症における血小板凝集抑制薬や抗凝固薬の果たす役割は大きく、代表的な薬物にアスピリン、ヘパリ

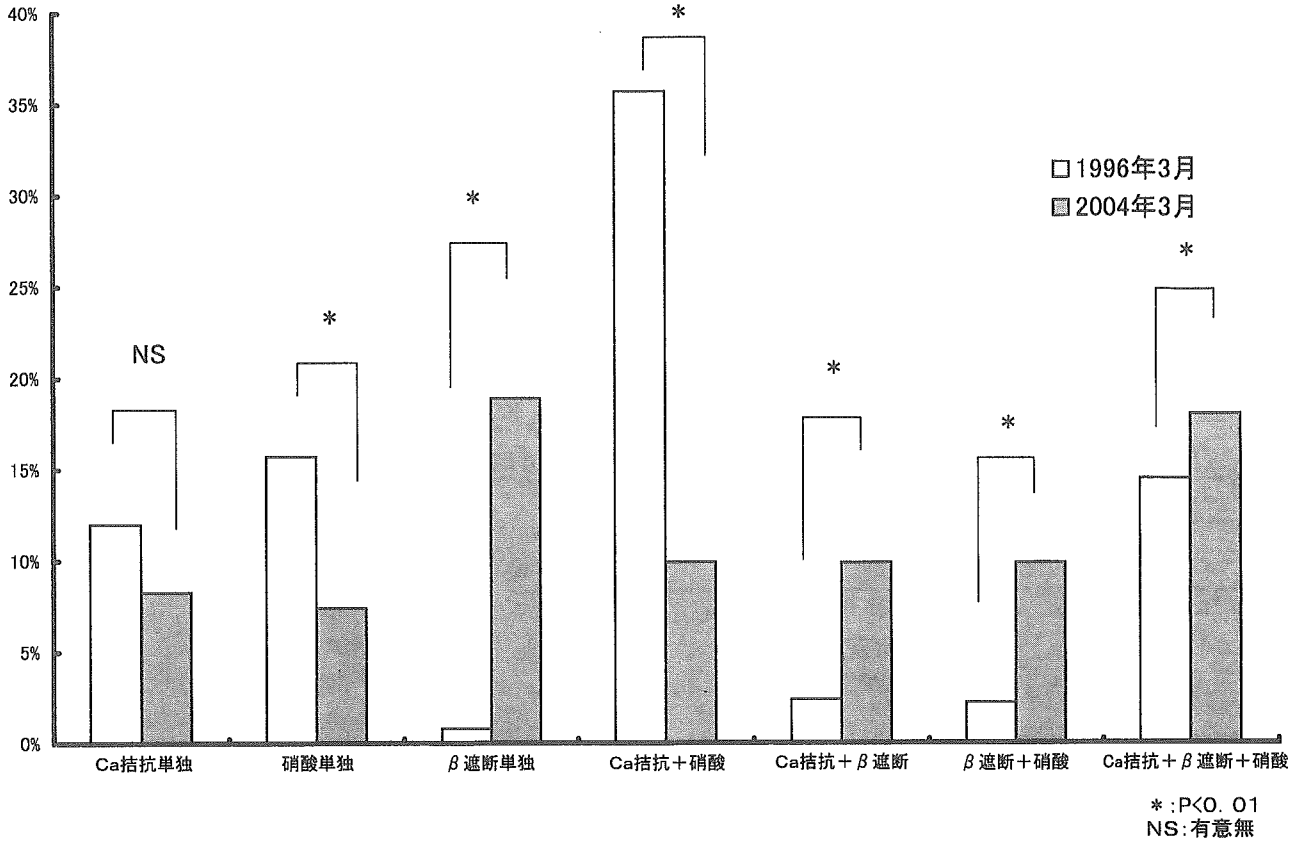


Fig. 2. 抗狭心症薬の併用状況

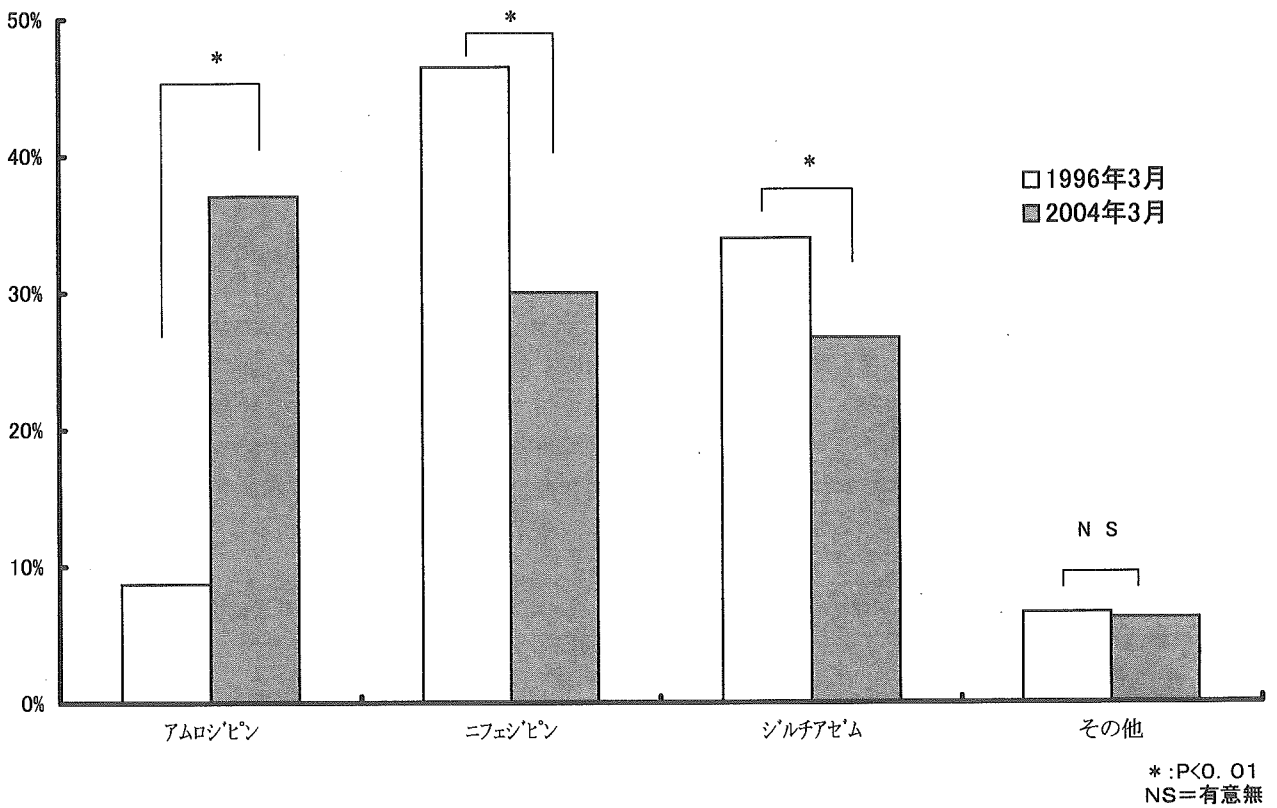


Fig. 3. Ca拮抗薬の使用状況

Table 2. 1996年3月と2004年3月の $\beta$ 遮断薬使用状況の比較

分類	一般名	1996年	2004年	
1群: $\beta_1$ non selective・ISA(-)	プロプラノロール	30名	7名	
		18%(30名)	1.3%(7名)	*
2群: $\beta_1$ non selective・ISA(+)	塩酸カルテオロール ピンドロール マロン酸ボピンドロール	11名	1名	
		3名	0名	
		1名	0名	
		9%(15名)	0.3%(1名)	*
3群: $\beta_1$ selective・ISA(-)	酒石酸メブプロロール アテノロール フマル酸ビソプロロール 塩酸ベタキソロール	62名	208名	
		30名	105名	
		12名	66名	
		2名	0名	
		63.5%(106名)	75.5%(379名)	*
4群: $\beta_1$ selective・ISA(+)	塩酸アセプトロール 塩酸セリプロロール	2名	0名	
		2名	0名	
		2.4%(4名)	0%(0名)	NS
5群: $\alpha$ $\beta$ blocker	カルベジロール 塩酸アロチノロール 塩酸ラベタロール	5名	136名	
		4名	3名	
		3名	0名	
		7.2%(12名)	22.4%(139名)	*
合計		167名	526名	*

\*  $p < 0.01$  NS = 有意無

ン、ワルファリンがある。特にアスピリンは虚血性心疾患の一次予防に有効であるとともに、心筋梗塞二次予防効果についても多くの臨床試験においてその有効性が確立され、禁忌でないかぎり発症直後の症例から長期間にわたり心筋梗塞患者全例に用いるべきであるとされている<sup>15)</sup>。「循環器病の診断と治療に関するガイドライン(1998-1999年度合同研究班報告)心筋梗塞二次予防に関するガイドライン」<sup>1)</sup>や「AHA/ACC動脈硬化性心血管疾患患者の二次予防ガイドライン2001改訂」にも記載されており<sup>2)</sup>、今回の調査で処方量が増加したと考えられる。また、1996年には低用量アスピリン製剤である小児用バファリン<sup>®</sup>が血栓・塞栓症に適応がなかったが、2000年に心筋梗塞の血栓・塞栓抑制に適応のあるバイアスピリン<sup>®</sup>錠(バイエル薬品株)やバファリン81<sup>®</sup>(ライオン株)が発売されたのも一因と考えられた。

ACE阻害薬については、心筋梗塞発症後における有効性を示す論文は多く存在し<sup>16,17)</sup>、リモデリングの予防や心不全の予防を目的として早期から使用される薬物である。心筋梗塞発症早期よりリモデリングを抑制するACE阻害薬<sup>3,4)</sup>やARBが有効である<sup>5)</sup>ことが知られており、予後に関するエビデンスとしてACE阻害薬では、SAVE<sup>6)</sup>、AIRE<sup>6)</sup>およびTRACE<sup>7)</sup>などがあり、ARBではVALIANT<sup>8)</sup>など数々の報告がある。ただし、ARBの適応に心不全の適応はなく、ACE阻害薬も一部は同様に高血圧症のみの適応である。「AHA/ACC動脈硬化性心

血管疾患患者の二次予防ガイドライン2001改訂」では、高リスク症例(広範心筋梗塞症、心不全合併例、心筋梗塞既往例など)の急性期離脱後に投与開始し、左室駆出率(EF)低下例(<40%)、心不全合併例は慢性期にも継続投与するとされており<sup>1)</sup>処方数が増加しているとの考えられた。また、1996年調査時にはARBは、発売されておらずACE阻害薬で空咳等の副作用などが生じた場合に中止せざるを得なかった症例が、ARBへの変更も可能となったことが心筋梗塞症でも投与されている一因と考えられる。

抗狭心症薬の使用状況については、1996年は硝酸薬を中心に使用される傾向にあったが、硝酸薬は血行再建後の患者で残存虚血のない例では投与の意義がないとする報告があり<sup>18,19)</sup>、他に有意病変があるときのみに硝酸薬が併用されるようになったため減少したのと考えられ2004年では $\beta$ 遮断薬を中心として使用される傾向にある。

Ca拮抗薬の作用には、冠血管拡張作用や心筋収縮抑制作用や末梢血管拡張作用があり、特に冠攣縮性狭心症には、Ca拮抗薬が第一選択薬として用いられている。1996年に比べ2004年のアムロジピンの使用が増加した。アムロジピンは、Ca拮抗薬の中で相互作用が最も少なくニフェジピンと比べて反射性頻脈を起こしにくく、最高血中濃度と最低血中濃度の差が小さく安定した効果を有し、また交感神経の亢進やレニン-アンジオテ

ンシン系の亢進は認められていない<sup>20)</sup>。PREVENT 試験<sup>9)</sup>の結果では心筋梗塞や心臓関連死などのイベントの減少を認めるまでには至っていないが、冠動脈疾患患者における不安定狭心症や血行再建術などは有意に抑制した。また、アムロジピンは心不全患者の予後に悪影響は及ぼさないため心機能低下症例に対しても使用され増加したものと考えられた。CAMLOT 試験<sup>21)</sup>においてアムロジピンは心血管系イベント抑制効果が確立している ACE 阻害薬と同等あるいはそれ以上の効果が報告されていることや冠動脈におけるアテローム性動脈硬化病変の進展抑制も認められたことから、冠攣縮を伴う患者が多い日本人には冠攣縮抑制に関するエビデンスはないものの、今後も高頻度に使用される可能性がある。また、野々木らは長時間作用型のニフェジピンが ACE 阻害薬による治療と同様に冠血管事故を減少させ死亡率を低下させたことと JMIC-B で報告している<sup>22)</sup>。ジルチアゼムに関しては非 Q 波梗塞後の早期再梗塞および重症狭心症の予防に有効であることが報告されたが<sup>23)</sup>、左室機能不全やうっ血性心不全あるいは房室ブロックがない患者には特に用いるべきではないと考えられている。最近報告された INTERCEPT 試験<sup>24)</sup>では血栓溶解療法後の急性心筋梗塞患者において、ジルチアゼムが心事故を低下させる傾向があるといわれており使用頻度の減少があまりみられなかったとも考えた。また、他の薬物でコントロールができない狭心症や高血圧症を合併する心筋梗塞症患者で用いられたことも考えられた。

$\beta$  遮断薬の心事故防止に及ぼす効果として、心筋酸素消費量削減(血圧・心拍数・収縮力の低下)、抗不整脈作用および心筋虚血改善作用がある。 $\beta_1$  選択性のものは心臓以外への作用は少なく副作用が少ない利点があり、Soriano ら<sup>25)</sup>の集計では $\beta_1$  選択性、ISA(-)、膜安定化作用(-)で脂溶性の $\beta$  遮断薬メトプロロールが心事故防止に及ぼす効果が明らかであるとしている。ただし、高齢者や合併症(気管支喘息・心不全・糖尿病・徐脈・房室ブロック・閉塞性動脈硬化症)がある場合に使用しにくいことや、また欧米に比べて日本人に冠動攣縮が多いと考えられているために<sup>26)</sup>第1選択薬になりにくいことが考えられた。しかし、 $\beta$  遮断薬については冠攣縮があってもごく少量から慎重に他の薬物主に Ca 拮抗薬と併用していくことにより、長期的に評価すれば $\beta$  遮断薬の心保護作用が、生命予後改善を期待できると考えられている。また、糖尿病や高脂血症合併例においても、 $\beta$  遮断薬により糖代謝および脂質代謝は多少悪化するが、長期的にはそうしたマイナス面をはるかにしのぐ生命予後改善効果を期待しうると考えられている。 $\beta$  遮断薬では主に1980年代に多数の臨床試験が行われ、代表的なものとして、メトプロロールの早期効果を検討した MIAMI<sup>10)</sup> や TIMI II B<sup>12)</sup>、アテノロール早期効果を検討した ISIS-

1<sup>11)</sup>などいずれの臨床試験においても心筋梗塞の予後の改善効果が報告されている。そして、1984年の Goteborg Metoprolol Trial<sup>13)</sup>では、 $\beta_1$  選択性 ISA(-)のメトプロロールにより、心筋梗塞の予後を短期的にも長期的にも改善することが実証され、投与される患者の増加も示唆された。また、近年では、CHAPS(Carvedilol Heart Attack Pilot Study)試験において<sup>27)</sup>、駆出率45%以下の患者でカルベジロール群はプラセボ群に比べ心イベント発症率が42%と有意に低下し、カルベジロール群におけるイベント発症率の低さは投薬開始直後より明らかであった。また、心筋梗塞症後の心リモデリングに関してもプラセボに比べカルベジロール群で有意な抑制作用が確認されている。「AHA/ACC 動脈硬化性心血管疾患患者の二次予防ガイドライン2001改訂」では<sup>2)</sup>低リスク群以外の心筋梗塞(急性期および陈旧性のもの)、梗塞後狭心症、重症心室性不整脈、高血圧症合併例、急性期の左心不全合併例および梗塞範囲の大きい例への投与が推奨されている。また、2001年3月に米国心臓病学会で報告された CAPRICORN(Carvedilol post infarct survival control in LV dysfunction) study<sup>14)</sup>では、左室機能低下例でも $\beta$  遮断薬が有効であることが明らかにされ、注目された。すなわち、心筋梗塞後重急性期の $\beta$  遮断薬投与により、左室機能低下例の総死亡は23%減少し、プラセボ群より有意であったことが報告された<sup>15)</sup>。CHAPS、CAPRICORNの結果は、ともに心筋梗塞後、すでに血栓溶解療法あるいは ACE 阻害薬の投与を受けている左室不全患者に対して、 $\beta$  遮断薬を追加・併用することで予後改善、心血管イベント発症が抑制されることを示すものであった。今回、2004年の解析ではこれらエビデンスにより $\beta$  遮断薬の投与が増加したものと考えられる。また、カルベジロールについては2002年12月に低心機能例の心不全患者へ適応追加されたことや、抗酸化作用や $\alpha_1$  遮断作用を併せ持つことが処方頻度増加の原因であると考えられた。今後は再還流後の $\beta$  遮断薬の有効性に関するデータが望まれる。

2004年では血小板凝集抑制薬、 $\beta$  遮断薬、ACE 阻害薬および ARB の処方頻度の増加が認められた。特に血小板凝集抑制薬は90%を超える患者に処方されており、そのほとんどがアスピリン製剤であった。1996年および2004年の両年において高い頻度の多剤併用が認められていたが、その中心的薬剤は、硝酸薬から $\beta$  遮断薬中心へと移行していた。その $\beta$  遮断薬において $\beta_1$  選択的 ISA(-)と $\alpha\beta$  遮断薬が中心的な位置を占めていた。また、カルシウム拮抗薬におけるアムロジピンの使用頻度はこの8年間に増加傾向を示していた。そして、今回の処方調査の結果、当センターでは、心筋梗塞症に対する薬物療法において、エビデンスやガイドラインに基づく標準的な治療がなされていると考えられた。

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## Two Adults Requiring Implantable Defibrillators Because of Ventricular Tachycardia and Left Ventricular Dysfunction Caused by Presumed Kawasaki Disease

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There is an adult patient population in Japan with undiagnosed coronary artery lesions caused by Kawasaki disease (KD) occurring before 1967, the time at which KD was first described. Two adult patients presented with a low left ventricular (LV) ejection fraction and ventricular tachycardia (VT) caused by presumed KD. A 43-year-old man with rapid VT had a history of an acute febrile illness with desquamation of the fingertips at the age of 10 months. Coronary angiography (CAG) showed segmental stenosis of the right coronary artery (RCA) and occlusion of the left anterior descending artery with a giant aneurysm. The other patient was a 48-year-old man with a history of ischemic cardiomyopathy diagnosed after a previous myocardial infarction when he was 32 years old. He had segmental stenosis of the RCA on CAG. Non-sustained VT with transient unconsciousness was observed during 24-h Holter electrocardiography. Rapid VT with syncope was induced in both patients in the electrophysiologic studies and an implantable defibrillator was required to prevent sudden death. Physicians must be aware that VT can occur in older patients with LV dysfunction many years after KD. (*Circ J* 2005; 69: 870–874)

**Key Words:** Coronary artery disease; Implantable defibrillator; Kawasaki disease; Left ventricular dysfunction; Non-sustained ventricular tachycardia

**K**awasaki disease (KD) is an acute febrile infantile disease, first described in 1967<sup>1</sup>, but there is an adult patient population in Japan with a history of acute KD and cardiac sequelae occurring before 1967<sup>2</sup>. In most of these patients, the coronary artery lesions caused by KD were first recognized after an acute myocardial infarction or at autopsy for sudden death<sup>3–8</sup>. We present 2 adult patients with ventricular tachycardia (VT) and left ventricular (LV) dysfunction caused by coronary artery lesions after presumed KD.

### Case Reports

#### Case 1

In 1993 a 34-year-old man visited hospital because of headache. A 12-lead electrocardiography (ECG) revealed an abnormal Q wave in lead III and a QS pattern in V<sub>1</sub> and V<sub>2</sub>. Coronary angiography (CAG) showed segmental stenosis of the right coronary artery (RCA) and occlusion of the left anterior descending artery (LAD) with calcification of a giant aneurysm. At the age of 10 months, he had had an episode of unexplained fever lasting 1 month with desquamation of the palms and fingertips. He was diagnosed in 1993 as having coronary artery lesions caused by KD. Multifocal premature ventricular contractions (PVC) were frequently observed in on 24-h Holter ECG. Furthermore, he had a low LV ejection fraction (LVEF). Beta-

blocker was prescribed. At the age of 43 years, he visited another hospital because of fever associated with a common cold. An ECG revealed wide QRS tachycardia at a rate of 198 beats/min (Fig 1), as well as left axis deviation and right bundle-branch block. He was restored to normal sinus rhythm by direct conversion and was referred to us. Body length and body weight were 169 cm and 74 kg, respectively; blood pressure was 130/80 mmHg; total cholesterol was 228 mg/dl. At cardiac catheterization, the LV end-diastolic volume (LVEDV) and LVEF were 97 ml/m<sup>2</sup> and 41%, respectively. The CAG findings were similar to the previous imaging (Fig 2). Electron beam computed tomography showed the occlusion of the LAD with calcification of a giant aneurysm. He underwent coronary artery bypass grafting to the RCA and LAD. Amiodarone was prescribed. During electrophysiologic studies (EPS), 2 clinical and 2 non-clinical episodes of VT were induced in the left postero-septal wall of the left ventricle and a diastolic potential was recorded at the site. Radiofrequency catheter ablation was successful for 3 of the 4 foci. However, it was impossible to ablate the focus inducing rapid VT with syncope, so an implantable defibrillator (ICD) was inserted.

#### Case 2

In 1987, a 32-year-old man visited hospital because of general malaise. He was diagnosed as having ischemic cardiomyopathy after a previous myocardial infarction (MI). There was segmental stenosis of the right coronary artery on CAG but an almost normal left coronary artery. Multifocal PVC and couplets were detected on 24-h Holter ECG. He had experienced palpitations and transient unconsciousness 2 or 3 times since then. When 48 years old, he experienced presyncope with a cold sweat and an oppressive

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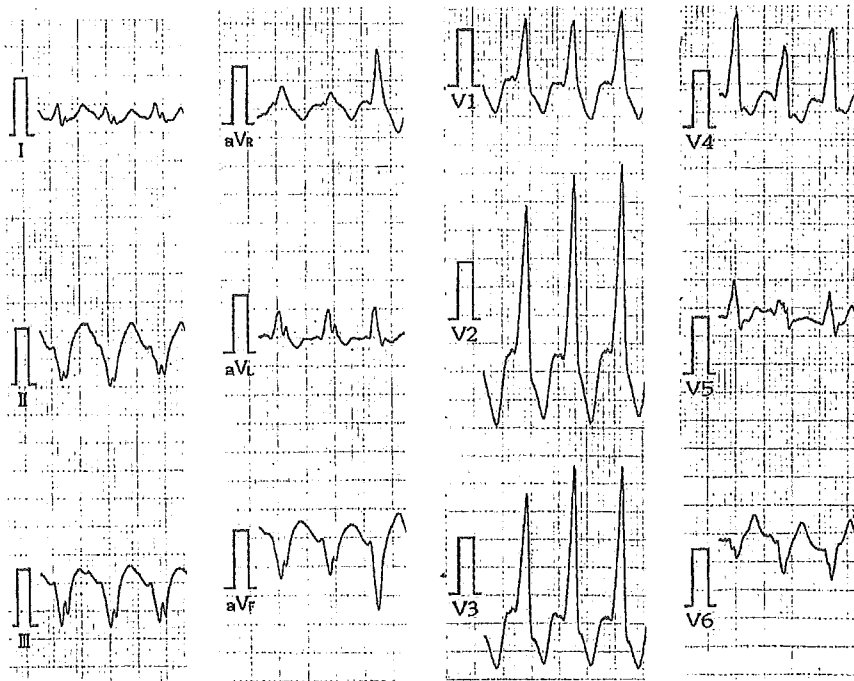


Fig 1. 12-lead ECG of wide QRS tachycardia of 198 beats/min. The ECG shows the left axis deviation and right bundle-branch block.

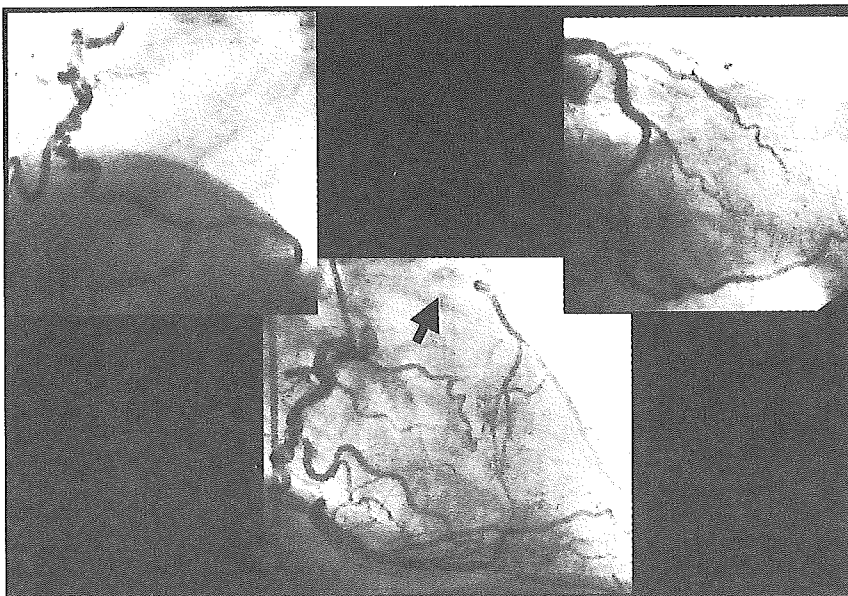


Fig 2. Case 1: Coronary angiogram shows segmental stenosis of the right coronary artery (Left). (Middle) The left anterior descending artery filled via collateral arteries from the right coronary artery (arrow shows a giant calcified aneurysm of the left anterior descending artery). (Right) The left anterior descending artery is occluded.

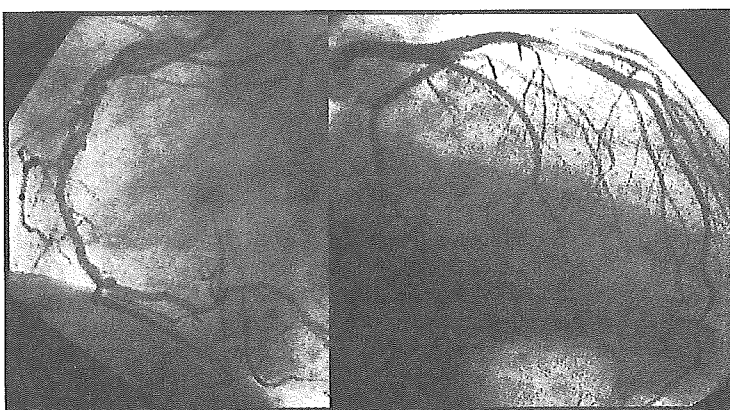


Fig 3. Case 2: Coronary angiogram shows segmental stenosis of the right coronary artery (Left) and an almost normal left anterior descending artery (Right).



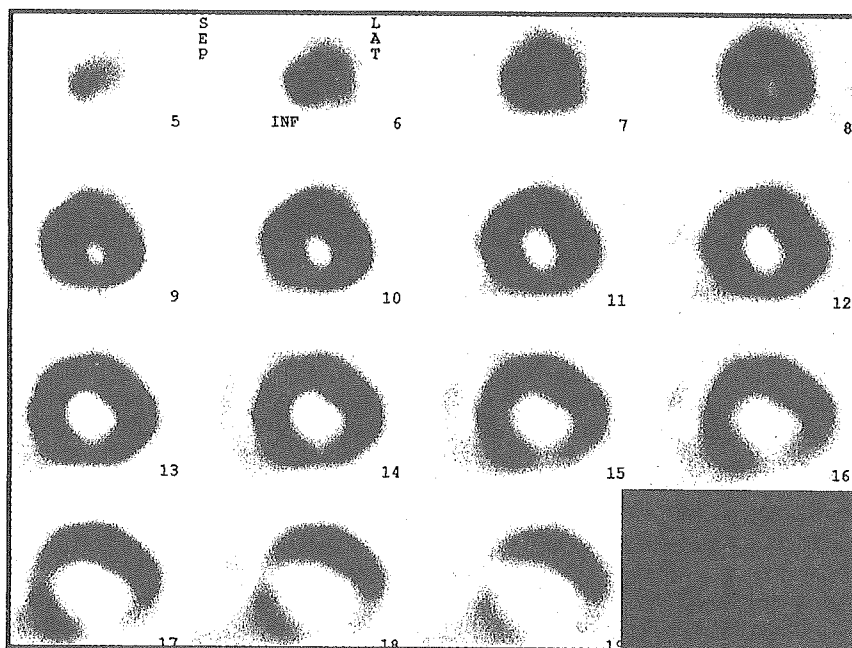


Fig 4.  $^{99m}\text{Tc}$ -MIBI myocardial imaging at rest (short-axis view).

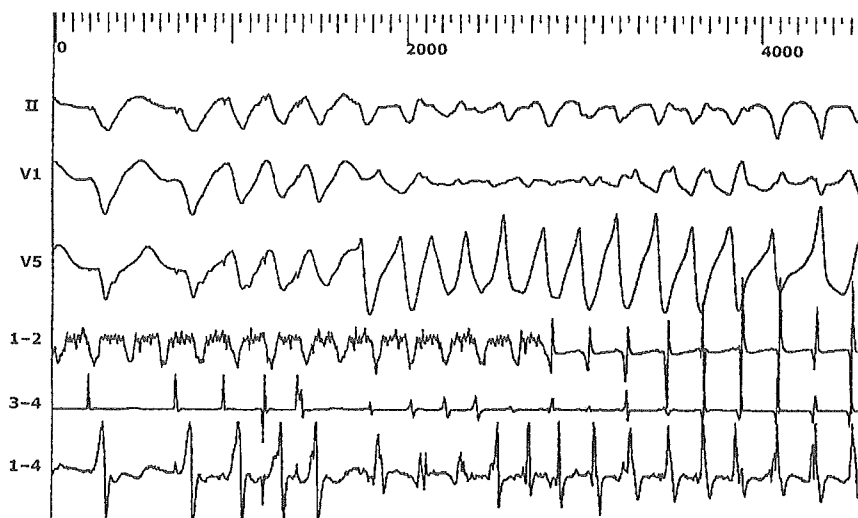


Fig 5. Rapid ventricular tachycardia (VT) with syncope during the electrophysiologic study. Polymorphic VT was induced by stimulation at the apex of the right ventricle, and it evolved into rapid VT with syncope.

sensation in his chest immediately after getting up during the night. Non-sustained VT (NSVT) including a 19-beat run was observed during 24-h Holter ECG and he was referred to us. Body length and body weight were 163 cm and 73 kg, respectively; blood pressure was 120/60 mmHg; total cholesterol was 196 mg/dl while taking 3-hydroxy-3-methyl-coenzyme A reductase inhibitor. He had given up smoking when 32 years old. ECG revealed an abnormal Q wave in lead III, poor progression of the r wave in V<sub>1</sub> and V<sub>2</sub>, and flat T waves in V<sub>5</sub> and V<sub>6</sub>. An episode of acute KD was unknown. LVEDV and LVEF were 147 ml/m<sup>2</sup> and 32%, respectively, on left ventriculography. The CAG findings were almost the same previously (Fig 3). A perfusion defect in the inferior wall of the left ventricle was found on  $^{99m}\text{Tc}$ -methoxy-isobutyl isomitrile myocardial imaging at rest (Fig 4). The histologic findings of a biopsy of the right ventricle did not correspond to that of any cardiomyopathy. Beta-blocker was prescribed. At EPS, monomorphic NSVT at a rate of 240 beats/min with left axis deviation and polymorphic VT of several beats run were induced by stimula-

tion at the outflow tract of the right ventricle. They stopped spontaneously, and he had presyncope at the time. Furthermore, polymorphic VT was induced by stimulation at the apex of the right ventricle, and it evolved into rapid VT (Fig 5). He collapsed, but was restored to normal sinus rhythm by direct conversion. He had no abnormal potentials at the apex of the right ventricle in sinus rhythm; however, ICD implantation is planned to prevent sudden death.

## Discussion

KD is an acute febrile disease affecting children, mainly those less than 5 years of age.<sup>9</sup> Currently in Japan, approximately 6,000–8,000 patients develop KD each year. Its cause remains unknown, but it is a systemic vasculitis involving medium-sized vessels. Diagnosis is based on the major clinical features of acute KD, which include fever of at least 5 days duration, bilateral conjunctival injection, an erythematous reaction involving the lips and oral cavity,

polymorphous exanthema, cervical lymphadenopathy, erythema of the palms and soles and/or firm induration of the hands or feet in the early phases and desquamation of the fingers and toes in the post-inflammation period!<sup>9</sup> All these symptoms are self-limiting and not all occur in every patient. In addition, the severity of the symptoms varies and for these reasons the diagnosis of KD can be difficult. Acute systemic arteritis particularly affects the coronary arteries. In the 1970s, it was considered that approximately 20% of acute KD patients had cardiac sequelae immediately after the acute illness;<sup>10</sup> however, it was difficult to diagnose both acute KD and the development of coronary artery lesions at that time. Most patients with coronary artery lesions caused by KD are asymptomatic until acute myocardial infarction or sudden death occurs and there are probably many asymptomatic adult patients with coronary arterial lesions caused by KD who remain undiagnosed.

The present 2 patients had coronary artery lesions and a low LVEF diagnosed when they were in their 30s. Both had segmental stenosis of the RCA, which is often found in patients with a history of KD and is considered typical of the lesions caused by the disease. It implies the development of several new small vessels, reflecting recanalization after coronary artery occlusion!<sup>10,11</sup> Because approximately two-thirds of patients with segmental stenosis or complete coronary occlusion are asymptomatic, coronary artery occlusion cannot be diagnosed without CAG!<sup>2</sup> and consequently, LV dysfunction after MI can exist unrecognized for many years in such patients. As a result, they are asymptomatic for many years after the episode of undiagnosed acute KD!<sup>13</sup> The 2 patients described here developed VT when in their 40s and it was most likely secondary to myocardial damage after a previous MI. We believe that VT develops with age, many years after the previous MI.

Giant aneurysms in the proximal portion of the coronary arteries are a characteristic coronary artery lesion caused by KD!<sup>0</sup> and they often develop late calcification on the outer surface. Case 1 had an occluded and calcified giant aneurysm of the LAD. Stenotic lesions and calcification involving the same segments in which the coronary aneurysms develop occur during the acute phase of KD. Furthermore, affected segments and almost normal segments may be found in the 1 patient!<sup>4</sup>

These 2 patients were born in the 1950s. The mother of Case 1 remembered the symptoms of his acute illness in infancy, which were consistent with acute KD. Any history of an acute illness in childhood was unknown in the other patient. However, we suspect that the characteristic coronary artery lesions and ischemic cardiomyopathy occurring in middle-age of individual without high risk of atherosclerosis signify a KD etiology.

Adults with ischemic cardiomyopathy, severely depressed LV function, and asymptomatic NSVT are at significant risk for future arrhythmic events!<sup>5</sup> Sudden death occasionally occurs in their 20s in patients with LV dysfunction and NSVT after KD!<sup>6,17</sup> In such cases there was probably an undiagnosed MI soon after the onset of KD and they then remained asymptomatic prior to their sudden death. We suspect that fatal arrhythmias in such patients are a late complication of MI,<sup>3,18,19</sup> which might occur earlier in KD patients with a low LVEF than in adults with LV dysfunction caused by atherosclerosis.

Treatment for KD patients with long-standing LV dysfunction after previous MI becomes more essential as they get older. An EPS and then antiarrhythmic treatment will

be required to prevent sudden death. If critical VT is detected, catheter ablation or implantable cardioverter-defibrillator should be considered<sup>20,21</sup> because patients with severe coronary artery lesions caused by KD are likely to have cardiac events earlier than the normal population.

## Conclusion

There is a population of adults in Japan with undiagnosed coronary arterial lesions caused by KD. They can be recognized by an episode of ventricular arrhythmia and a low LVEF, as well as by acute MI or sudden death. Detection and treatment of such KD patients is essential to prevent premature death.

## Acknowledgments

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# Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation

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## KEYWORDS

Echocardiography;  
Extracorporeal circulation;  
Myocarditis;  
Shock

**Aims** The clinical outcome of severe acute myocarditis patients with cardiogenic shock who require circulatory support devices is not well known. We studied the survival and clinical courses of patients with fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation (ECMO) and compared them with those of patients with acute non-fulminant myocarditis.

**Methods and results** Patients with acute myocarditis were divided into the following two groups. Fourteen patients who required ECMO for cardiogenic shock were defined as having fulminant myocarditis (F group), whereas 13 patients who had an acute onset of symptoms, but did not have compromised, were defined as having acute non-fulminant myocarditis (NF group). In the F group, 10 patients were weaned successfully from percutaneous ECMO. Therefore, the overall acute survival rate was 71%. Patients who were not weaned from ECMO showed smaller left ventricular end-diastolic and end-systolic dimensions, thicker left ventricular wall, and higher creatine phosphokinase MB isoform levels than those who were weaned from ECMO. When compared with patients in the NF group, the fractional shortening in the F group was more severely decreased in the acute phase [F:  $10 \pm 4$  vs. NF:  $23 \pm 8\%$  (mean  $\pm$  SD),  $P < 0.001$ ], but recovered in the chronic phase (F:  $33 \pm 7$  vs. NF:  $34 \pm 6\%$ ). The prevalence of adverse clinical events in both groups was similar during the follow-up period of 50 months. **Conclusion** In patients with fulminant myocarditis, percutaneous ECMO is a highly effective form of a haemodynamic support. 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.

## Introduction

Myocarditis is defined as an inflammation of the myocardium caused by viral, rickettsial, bacterial or protozoal infections, or drug toxicity.<sup>1–3</sup> Its clinical features vary, ranging from asymptomatic secondary to focal inflammation to fulminant fatal congestive heart failure. Moreover, there is a possibility that viral myocarditis may lead to dilated cardiomyopathy, presumably as a consequence of a late immunological response.<sup>2</sup> Patients with fulminant myocarditis often present with cardiogenic shock due to a severe left ventricular dysfunction.

Critically ill patients often require mechanical circulatory support such as a percutaneous extracorporeal membrane oxygenation (ECMO) with a cardiopulmonary bypass. Some studies showed that mechanical circulatory support is effective and can eliminate the need for cardiac transplantation

in patients with cardiogenic shock secondary to fulminant myocarditis. These studies further showed an overall survival rate range of 50–70%, in the case of using mechanical circulatory support, is possible either by cardiac recovery or by transplantation.<sup>4–7</sup> These studies showed that the survival rate in the case of using percutaneous ECMO is higher than that in using a ventricular assist device.<sup>6</sup> This result may be due to the quick and easy application of percutaneous ECMO preventing multiple organ failure secondary to haemodynamic deterioration, when compared with a ventricular assist device. McCarthy *et al.*<sup>8</sup> demonstrated that patients with lymphocytic fulminant myocarditis have a better prognosis than those with acute non-fulminant myocarditis, providing important information for a better understanding of the pathophysiology of myocarditis. However, in their study, only two of 15 patients with fulminant myocarditis were treated with mechanical circulatory support. The clinical outcome of critical myocarditis patients with cardiogenic shock who require circulatory support devices is not well known. Thus, in the present

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study, we have focused on the survival and clinical courses of severely ill patients who are under mechanical circulatory support with percutaneous ECMO and compared them with those of patients with acute non-fulminant myocarditis.

## Methods

### Clinical classification

The diagnosis of myocarditis was made on the basis of the following findings: (i) a recent medical history consistent with the occurrence of a viral infection, (ii) positive findings of inflammation (high fever and increased white blood cell count and C-reactive protein level), (iii) evidence of myocardial damage [significant changes in electrocardiographic and echocardiographic features and elevations of serum creatine phosphokinase (CPK) and its MB isoform (CK-MB) level], and (iv) signs of a recent onset of cardiac dysfunction that were not due to myocardial ischaemia (determined by coronary angiography). Patients who had signs of myocarditis associated with other systemic diseases, such as immunodeficiency, sarcoidosis, collagen diseases, endocrine diseases, drug-induced toxicity, or alcoholism, were excluded. Cardiogenic shock was defined on the basis of the criteria set by the Myocardial Infarction Research Units of the National Heart and Lung Institute.<sup>9</sup>

In the present study, patients with fulminant myocarditis were defined as those who require percutaneous ECMO or a ventricular assist device for cardiogenic shock and do not respond to intensive medical treatments like high doses of intravenous catecholamines or for refractory ventricular tachyarrhythmia. Patients with acute non-fulminant myocarditis were defined as those who had an acute onset of symptoms but did not have compromised haemodynamics following conventional medical treatment.

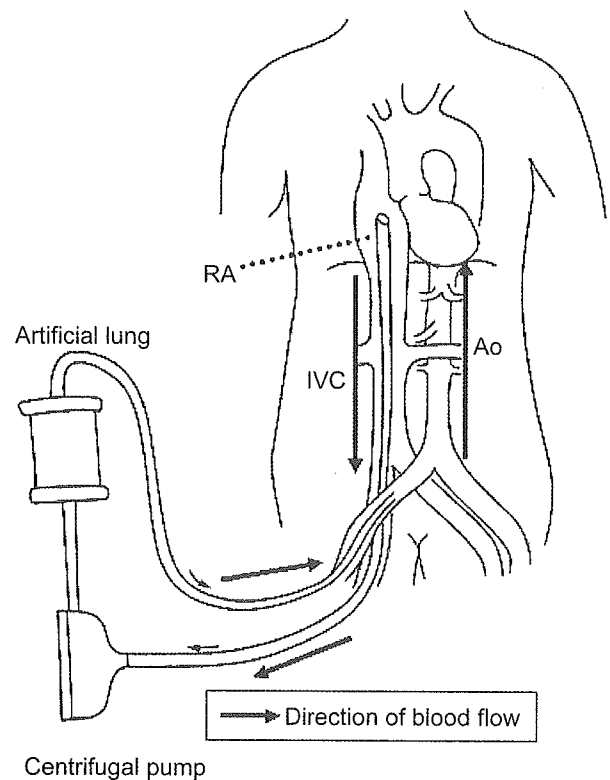
### Details of percutaneous ECMO system

A percutaneous ECMO system is basically a femoro-femora bypass without a reservoir (*Figure 1*). This system is completely pre-connected to a compact integrated cardiopulmonary bypass unit consisting of an artificial lung (Kurare Menox EL-4000) and a Sarns Delphin pump (Sarns 3M Healthcare, Ann Arbor, MI, USA). An oxygenator and a centrifugal pump are placed in the body of the compact integrated cardiopulmonary bypass unit as reported previously.<sup>10</sup> Heparin was used for anticoagulation and activated clotting time was maintained between 200 and 300 s.

### Study patients

Between January 1993 and December 2001, 27 patients were diagnosed as having acute myocarditis at the National Cardiovascular Centre (Japan). All patients except one had clinical symptoms and signs of acute myocarditis with a distinct onset (from days 2 to 28). The first application of percutaneous ECMO for patients with fulminant myocarditis was in June 1996. The distribution of year when the enrolled patients were admitted was as follows: F group: before 1995,  $n = 0$ ; 1996–98,  $n = 5$ ; 1999–2001,  $n = 9$ ; NF group: before 1995,  $n = 2$ ; 1996–98,  $n = 5$ ; 1999–2001,  $n = 6$ .

Fourteen patients, whose systemic blood pressure was low [ $74 \pm 15$  (mean  $\pm$  SD) mmHg] and heart rate was high ( $134 \pm 21$  b.p.m.; excluding two patients with cardiac arrest and using temporary right ventricular pacemaker) even after an intensive treatment with inotropic or vasopressor drugs, required percutaneous ECMO (F group) (male, seven; female, seven; mean age,  $38 \pm 15$ ). The remaining 13 patients whose blood pressure and heart rate were maintained at  $118 \pm 17$  mmHg and  $86 \pm 21$  b.p.m., respectively, were not treated with percutaneous ECMO (NF group) (male, 12; female, one; mean age,  $33 \pm 18$ ).



**Figure 1** Illustration of ECMO system. RA, right atrium; IVC, inferior vena-cava; Ao, aorta.

### Laboratory examination

On admission, blood samples were obtained every 3 h until the peak CPK and CK-MB levels were determined; thereafter, at least every 24 h until the patients recovered. Inflammation indexes (white blood cell count and C-reactive protein level), liver function (total bilirubin, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels), and renal function [blood urea nitrogen (BUN) and serum creatinine levels] were also analysed.

### Echocardiographic and haemodynamic measurements

Standard two-dimensional echocardiography (SONOS 5500, Phillips) was performed to assess the existence of pericardial effusion and to determine left ventricular end-diastolic dimension (LVDd), end-systolic dimension (LVDs), and wall thickness. These parameters of LV function were measured in the M-mode from the parasternal short-axis view using the leading-edge-to-leading-edge method. Fractional shortening (FS) was also calculated by a standard method.<sup>11</sup> Inferior vena-cava (IVC) diameters were measured from the long-axis two-dimensional subxiphoid views with the patients in a supine position to 30° upright position.<sup>12</sup> Flow across the valves was assessed by colour Doppler to grade the degree of mitral and tricuspid regurgitation. A 7.5 F Swan-Ganz thermodilution catheter (model: T-157A; Goodtech Inc.) was inserted through the internal jugular vein or the femoral vein to measure cardiac index, pulmonary capillary wedge, and right atrial pressures.

On admission, the data were obtained every 24 h until the patients were weaned successfully from the percutaneous ECMO system. During the period of using ECMO, we also measured LV ejection time corrected for  $\sqrt{RR}$  (LVETc). When LVETc improved to  $>200$  ms, ECMO flow rate was gradually decreased to 1.5 L/min, and ECMO was then discontinued if haemodynamics did not deteriorate.<sup>13</sup>

## Endomyocardial biopsy and postmortem autopsy

Endomyocardial biopsies were performed via the right internal jugular or femoral veins using disposable biotomes in surviving patients in stable conditions. Postmortem examination was also performed. At least four specimens were obtained from the right ventricular septum and immediately immersed in 10% formalin, embedded in paraffin, sectioned, stained with haematoxylin and eosin, and examined by a pathologist to determine whether myocarditis was present on the basis of the Dallas criteria.<sup>14</sup>

## Follow-up

After discharge, patients visited the hospital every 3–6 months. In the chronic phase (~6–12 months), echocardiography was performed to reassess LV function following myocarditis. The median period of chronic echocardiography was 12 months. Thereafter, follow-up data regarding death and cardiovascular events (e.g. rehospitalization due to congestive heart failure) were obtained from the medical records or telephone interviews of all patients.

## Statistical analyses

The values are presented as the mean  $\pm$  standard deviation (SD) or median (25–75%). The normality of distribution was assessed using the Kolmogorov–Smirnov test. Echocardiography and laboratory findings were compared between the two groups using the Student's *t*-test for normally distributed variables or the Mann–Whitney *U* test for other variables. To compare the proportions of patients, Fisher's exact test was performed. Comparisons of data using all these statistical tests were performed using Sigma Stat version 3.0 (SPSS, Chicago, IL, USA). All statistical tests were two-sided and significance was defined as  $P < 0.05$ .

## Results

### Comparisons between patients who were weaned and those who were not weaned from ECMO in the F group

Table 1 shows the summary of the patients' characteristics in the F group. The median time interval to ECMO application from the onset of heart failure was 15 (12–20) h (range: 7–36 h). Among the 14 patients in the F group (on ECMO support), a temporary right ventricular pacemaker was used in four patients (29%). In six patients (43%), intraaortic balloon pumping (IABP) had already been inserted because they had been transferred from other hospitals. Between patients with and without IABP, systolic blood pressure ( $75 \pm 17$  vs.  $73 \pm 15$  mmHg), own heart rate ( $127 \pm 17$  vs.  $138 \pm 22$  b.p.m.), LVDd ( $47 \pm 8$  vs.  $46 \pm 12$  mm), and FS ( $10 \pm 3$  vs.  $10 \pm 5\%$ ) were similar before ECMO application. Figure 2 shows acute changes in LV function before and immediately after the support and at the time of weaning from ECMO. Neither LVDd nor FS changed immediately after the ECMO support.

The median support time for percutaneous ECMO in the F group was 130 (42–171) h (maximum support time, 12 days). Four patients were not weaned from mechanical support and died. In one of them, the support system was changed to a left ventricular assist device (the Toyobo-NCVC-type pump)<sup>15</sup> because of the development of multiple organ failure despite ECMO support. Therefore, the acute survival rate was 71% in the F group.

We then compared the clinical characteristics between patients who were weaned and those who were not weaned from ECMO (Table 2). Although systemic

inflammation indexes (white blood cell count and C-reactive protein level) and liver function were similar, the peaks of CK-MB level and BUN level differed significantly between patients who were weaned and those who were not weaned from ECMO.

Figure 3 shows echocardiographic measurements for patients in the F group. Patients who were not weaned from ECMO had smaller LVDd ( $36 \pm 10$  vs.  $50 \pm 7$  mm,  $P = 0.013$ ) and LVDs ( $34 \pm 10$  vs.  $45 \pm 6$  mm,  $P = 0.026$ ) and thicker ventricular wall ( $15 \pm 1$  vs.  $11 \pm 2$  mm,  $P = 0.023$ ) than those who were weaned from ECMO. The left ventricular systolic function in patients who were not weaned from ECMO was more depressed than those who were weaned successfully, as shown by the difference in FS ( $5 \pm 4$  vs.  $11 \pm 4\%$ ,  $P = 0.036$ ).

### Comparison between F group and NF group

All the 13 patients in the NF group survived after the onset of acute myocarditis. IABP was used in one patient in the NF group. Inotropic agents were used under haemodynamic monitoring in five of 13 patients in the NF group and in 14 of 14 patients in the F group ( $P < 0.05$ ). The median doses of dopamine [NF: 0 (0–3.25) vs. F: 5.5 (3–15)  $\mu\text{g}/\text{kg}$  body weight/min,  $P = 0.002$ ] and dobutamine [NF: 0 (0–3) vs. F: 3 (3–10)  $\mu\text{g}/\text{kg}$  body weight/min,  $P = 0.017$ ] used were significantly lower for patients in the NF group than for those in the F group. There were significant differences in stroke volume index (NF:  $29 \pm 12$  vs. F:  $19 \pm 8$  mL/beat/m<sup>2</sup>,  $P = 0.048$ ), pulmonary capillary wedge (NF:  $15 \pm 6$  vs. F:  $23 \pm 5$  mmHg,  $P = 0.013$ ), and right atrial pressure (NF:  $8 \pm 4$  vs. F:  $14 \pm 6$  mmHg,  $P = 0.026$ ) between these two groups. FS assessed by echocardiography on admission was moderately depressed in patients in the NF group when compared with that in those in the F group ( $23 \pm 8$  vs.  $10 \pm 4\%$ ,  $P < 0.001$ ), although peak CK-MB levels and systemic inflammation indexes (e.g. white blood cell count and C-reactive protein level) were similar between these two groups (Table 3). Liver and renal functions were preserved in patients in the NF group, whereas these were impaired in patients in the F group.

### Follow-up study and clinical course

Endomyocardial biopsy or postmortem examination was performed at 25 (5.75–36.5) days in nine of 14 patients in the F group and at 14.5 (8.5–25.5) days in 12 of 13 patients in the NF group. The percentages of patients positive for myocardial infiltration by inflammatory cells were 78% (seven of nine patients) for the F group and 58% (seven of 12 patients) for the NF group. Moreover, as shown in Figure 4, echocardiography performed at the chronic stage (6–12 months) demonstrated that FS reversed dramatically in the F group reaching a similar level to that in the NF group (F:  $33 \pm 7\%$ , NF:  $34 \pm 6\%$ ), although LVDd did not change throughout the study.

Figure 5 shows the summary of the clinical course. The follow-up period was 50 (40–66) months for the F group and 66 (37–81) months for the NF group. Only one patient in the F group had congestive heart failure 14 months after the onset of acute myocarditis. None of the patients died or received cardiac transplantation in both groups.

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 <sup>2</sup> )	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 <sup>a</sup>	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.  
<sup>a</sup>Heart rate by temporary right ventricular pacing.

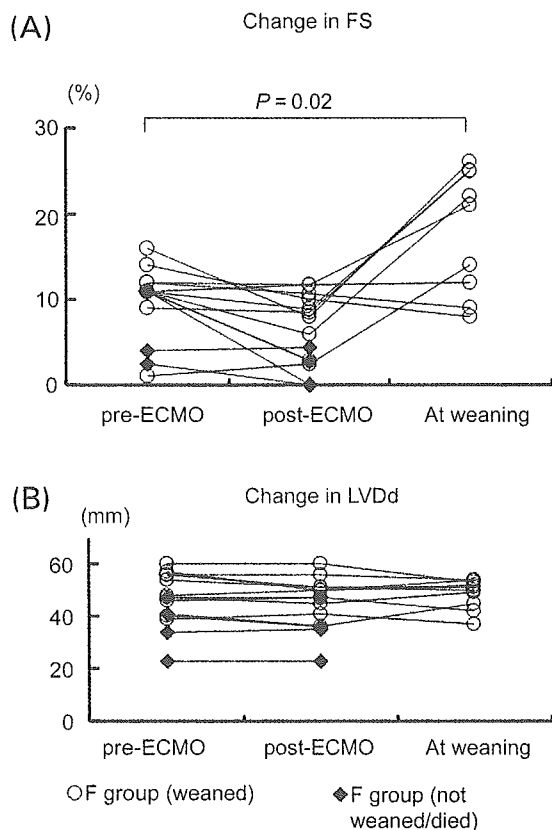


Figure 2 Acute changes in left ventricular function before and immediately after the support and at weaning from ECMO in patients with fulminant myocarditis (F group). (A) FS and (B) LVDD. Open circles indicate patients who were weaned from ECMO and closed diamonds indicate F patients who were not weaned 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.*<sup>8</sup> 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,<sup>4-6</sup> which may help in overcoming potential complications such as stroke, peripheral arterial ischaemia, haemorrhage, and

infections.<sup>16</sup> 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%.<sup>17</sup> 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.<sup>18</sup>

### 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.<sup>19,20</sup> 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)<sup>21-23</sup> and vaccination,<sup>24,25</sup> the use of which may provide new insights into the treatment of this disease. Duncan *et al.*<sup>7</sup> 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

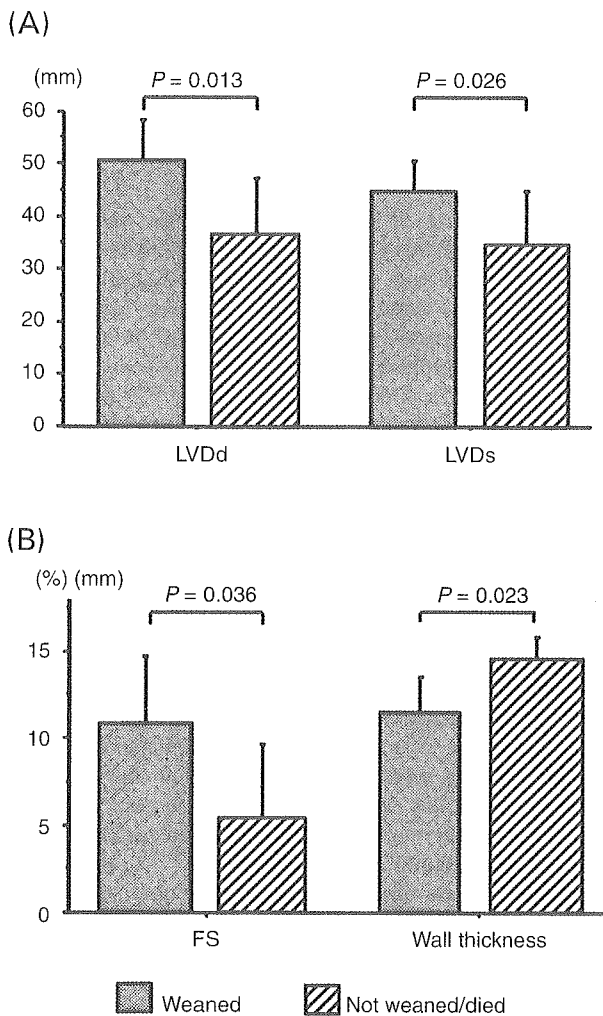
In patients with fulminant myocarditis who survived, FS improved in the chronic phase to a level similar to that in patients with acute non-fulminant myocarditis. The present results were different from those reported previously by Felker *et al.*<sup>26</sup> They reported a significant improvement in FS in patients with fulminant myocarditis (from  $19 \pm 4$  to  $30 \pm 8\%$ ), 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 (/ $\mu$ L)	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  $17 \pm 7$  to  $19 \pm 7\%$ ). 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.<sup>8,27,28</sup> 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.<sup>8,28</sup> In the previous studies, designed on the basis of the classification of Lieberman's report,<sup>29</sup> 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.*<sup>30</sup> 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.<sup>31</sup>

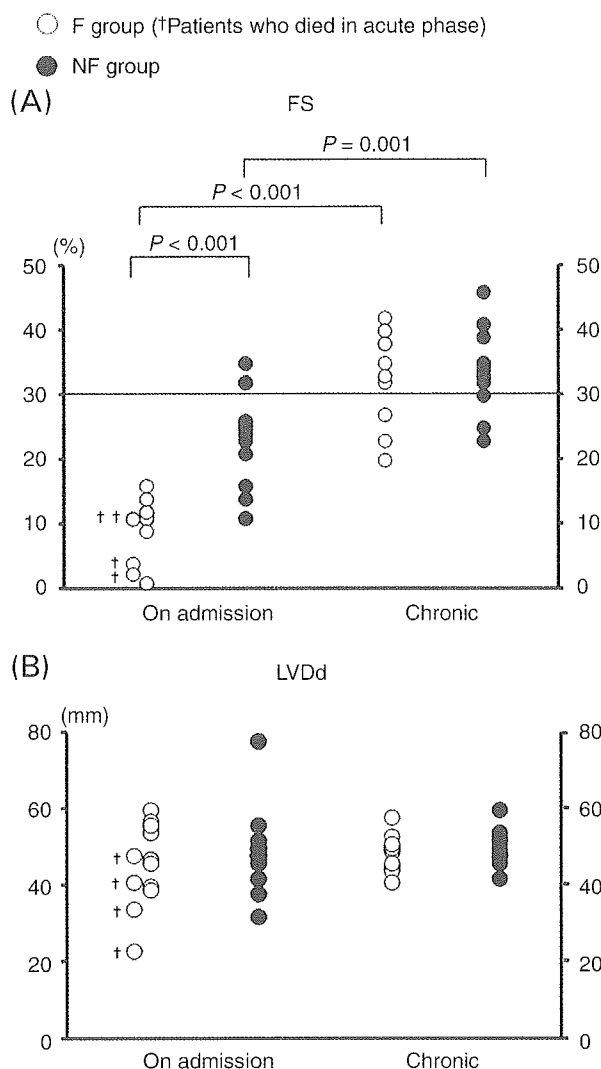
**Study limitations**

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.*<sup>32</sup> 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

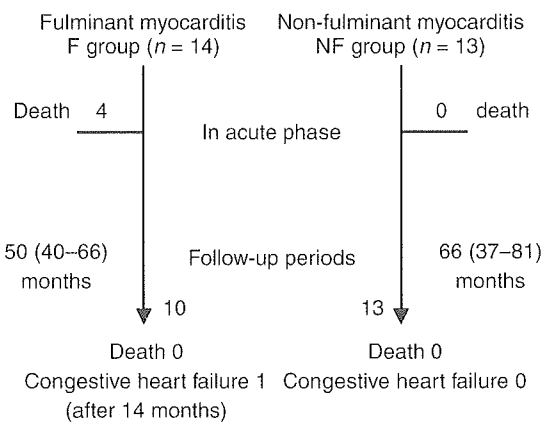
	F group (n = 14)	NF group (n = 13)	P-value
Aspartate aminotransferase (IU/L)	188 (108–381)	46 (39–127)	0.006
Alanine aminotransferase (IU/L)	70 (57–358)	42 (27–69)	0.051
Lactate dehydrogenase (IU/L)	711 (477–1229)	361 (175–491)	0.004
Peak CPK (IU/L)	3903 (1765–11667)	529 (253–1042)	<0.001
Peak CK-MB (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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心臓突然死の実態と今後の課題  
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## はじめに

わが国における心疾患による死亡は増加傾向にあり、成人の死因の第2位を占めている。心疾患による死亡はいわゆる突然死の形をとることが多く、わが国において心臓突然死は年間3~5万件発生しているともいわれている。percutaneous coronary intervention (PCI) をはじめとした心疾患に対するホスピタルケアは目覚ましい進歩を遂げ、急性心筋梗塞症の病院到着後の死亡率は10%以下にまで下がってきている。しかし、心臓突然死の最大原因とされる急性心筋梗塞症による死亡の半数から3分の2は病院外での心停止であると報告されている<sup>1,2)</sup>。心疾患による死亡を減少させるためには、病院外での心停止にも目を向け、プレホスピタルケアを充実させていく必要がある。

心臓突然死患者を救命するための条件を分かりやすく表現したものが chain of survival (救命の連鎖) であり、迅速な通報、迅速な心肺蘇生、迅速な除細動、迅速な二次救命処置の4つの輪からなる。中でも迅速な除細動が可能な救急システムの確立がもっとも重要視されており、AED (automated external defibrillator, 自動体外式除細動器) を用いた PAD (public access defibrillation, 市民による除細動) プログラムが欧米を中

心に導入され、その効果が数多く報告されている。わが国においても2004年7月に非医療従事者による AED の使用が認められ、AED の公共スペースへの配備が進んでいる。

本稿では、大阪府全域を網羅する形で病院外心停止症例に関するデータを集計しているウツタイン大阪プロジェクトで得られたデータにもふれながら、わが国における心臓突然死の実態と今後の課題について概説する。

## わが国における病院外心停止の実態

## 1. ウツタイン様式

ウツタイン様式は、病院外心停止症例の蘇生に関する記録を、国際的に標準化して行うために提唱されたガイドラインである<sup>3)</sup>。従来、病院外心停止症例に関する報告は多くの地域からなされてきたが、用語の定義も記録の方法も不統一であったために、それぞれの報告を客観的に比較・検討することができない状況が続いていた。そこで、ノルウェーの古い修道院である史跡ウツタインに蘇生に関連する専門家が集まり、提唱したものがこの様式である。ウツタイン様式では蘇生に関する用語を統一し、データの分析や提示の方法の標準化を勧めており、一定のテンプレートにあてはめて集計することにより、異なる地域間の蘇生に

[Key words] 病院外心停止, ウツタイン様式, bystander CPR, AED, PAD プログラム