

## Hemodynamics During Chronic Amiodarone Administration in Japanese Patients With Idiopathic Dilated Cardiomyopathy and Ventricular Arrhythmia: A Retrospective Study

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### Abstract

**Objectives.** Nonischemic heart disease, especially idiopathic dilated cardiomyopathy, is relatively common among Japanese patients receiving amiodarone for concomitant ventricular arrhythmia, but the hemodynamic effects of amiodarone in these Japanese patients are unclear. The hemodynamic changes during chronic amiodarone administration were retrospectively studied in patients with idiopathic dilated cardiomyopathy and ventricular arrhythmia.

**Methods.** Fifty-two patients [42 males, 10 females,  $53 \pm 2$  years (mean age  $\pm$  SE)] with ventricular tachyarrhythmia and idiopathic dilated cardiomyopathy with left ventricular ejection fraction of  $27 \pm 1\%$  (mean  $\pm$  SE) were treated with 200 - 400 mg daily of oral amiodarone as the loading dose for the initial 14 days and 100 - 200 mg daily maintenance dose for a further 6 months. No patients were taking beta-blockers or positive inotropic drugs. Echocardiographic examination was performed before (baseline), at week 2 and at month 6 of amiodarone therapy. Twenty four-hour Holter monitoring during the same time period was also performed in 34 patients. Seventeen patients underwent right heart catheterization before and at week 2.

**Results.** Echocardiographic measurements showed no significant change in left ventricular end-diastolic dimension, although there was a slight increase in fractional shortening from  $16 \pm 1\%$  to  $19 \pm 1\%$  ( $p < 0.05$ ) and  $18 \pm 1\%$  (mean  $\pm$  SE) ( $p < 0.01$ ) at week 2 and month 6 of amiodarone therapy, respectively. Amiodarone markedly reduced the mean heart rate and the frequency of premature ventricular complexes on ambulatory monitoring. The cardiac index did not change and the pulmonary capillary wedge pressure tended to decrease slightly at week 2 in the 17 patients who underwent catheterization.

**Conclusions.** This retrospective study showed no worsening of the hemodynamic state during chronic amiodarone administration in Japanese patients with idiopathic dilated cardiomyopathy and ventricular arrhythmia.

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### Key Words

■Amiodarone      ■Cardiomyopathy, dilated      ■Hemodynamics  
■Echocardiography, transthoracic      ■Ventricular function

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## INTRODUCTION

Amiodarone is an effective antiarrhythmic agent for the treatment of supraventricular and ventricular arrhythmias<sup>1</sup>), and is a major pharmacological option for the treatment of arrhythmia in patients with heart failure<sup>2</sup>). Amiodarone has a negative inotropic effect<sup>3</sup>), but chronic amiodarone treatment either has no effect or increases left ventricular ejection fraction in patients with obvious heart disease<sup>4-9</sup>). The majority of subjects in these studies were patients with left ventricular systolic dysfunction due to ischemic heart disease. In Japan, nonischemic heart disease, especially idiopathic dilated cardiomyopathy, is relatively common among patients receiving amiodarone for concomitant ventricular arrhythmia, and the dose and plasma level are lower than those in western countries<sup>10</sup>). However, little is known about the hemodynamic effects of amiodarone in Japanese patients with idiopathic dilated cardiomyopathy.

Beta-blocker administration is now the first-line therapy in patients with idiopathic dilated cardiomyopathy and potentially improves the hemodynamic state<sup>11-15</sup>). To assess the effect of amiodarone, we retrospectively investigated the hemodynamic changes during amiodarone therapy in patients with idiopathic dilated cardiomyopathy and ventricular arrhythmia, who were not being treated with beta-blockers or positive inotropic drugs.

## PATIENTS AND METHODS

This retrospective study included 52 patients with idiopathic dilated cardiomyopathy, 42 males and 10 females, aged 27 to 77 years [  $53 \pm 2$  years (mean age  $\pm$  SE) ] who had received amiodarone for treatment of nonsustained or sustained ventricular tachycardia or ventricular fibrillation at The Heart Institute of Japan, Tokyo Women's Medical University between 1988 and 1998. All patients had left ventricular systolic dysfunction on left ventriculography or radionuclide angiography with mean left ventricular ejection fraction of  $27 \pm 1\%$ , and were classified in New York Heart Association functional classes I to III. The basal rhythm was sinus rhythm in 49 patients and permanent atrial fibrillation in 3. Medical therapy, *e.g.* digoxin, diuretics, or vasodilators, was optimized so that all patients were clinically stable for at least 1 week before initiation of amiodarone treatment. We excluded patients receiving beta-blockers or other

antiarrhythmic drugs, or positive inotropic drugs except digoxin, those with decompensated heart failure, and those who developed apparent thyroid dysfunction. Patients received oral loading of amiodarone at a dose of 400 mg daily for 14 days. Administration was begun at 200 or 300 mg daily in some patients because of concomitant organic lung disease or reduced diffusion capacity of the lungs. After the initial loading phase, amiodarone was maintained at a dosage of 100 to 200 mg daily [  $132 \pm 6$  mg daily (mean dose  $\pm$  SE) ]

Echocardiographic examination was performed before (baseline), 2 to 3 weeks after (week 2) and 5 to 8 months (month 6) after initiation of amiodarone. The left ventricular end-diastolic dimension and the fractional shortening were measured on the two-dimensionally directed M-mode echocardiograms. Complete 24-hour Holter monitoring during the same time period was available in 34 of 52 patients. Seventeen of the 52 patients also underwent right heart catheterization before (baseline) and at week 2 of amiodarone therapy. Cardiac output was measured by the thermodilution technique. Written informed consent was obtained for all procedures.

Values are expressed as mean  $\pm$  SE. Hemodynamic and ambulatory electrocardiographic measurements during amiodarone therapy were compared with the baseline by using the Wilcoxon rank-sum test. A *p* value of  $< 0.05$  was considered statistically significant.

## RESULTS

The hemodynamic measurements, heart rate, and the frequency of premature ventricular complexes on Holter monitoring recorded at baseline, week 2 and month 6 of amiodarone therapy are listed in **Table 1**.

During amiodarone therapy, left ventricular end-diastolic dimension did not change, whereas fractional shortening was increased slightly, but significantly, at both week 2 and month 6. The cardiac index was unchanged at week 2, but the pulmonary capillary wedge pressure tended to decrease. The mean heart rate and the frequency of premature ventricular complexes on Holter monitoring were significantly reduced during amiodarone therapy.

## DISCUSSION

Our study observed no worsening of the hemodynamic state or left ventricular systolic function

**Table 1 Hemodynamic measurements, heart rate, and frequency of premature ventricular complexes at baseline and week 2 and month 6 of amiodarone therapy in patients with idiopathic dilated cardiomyopathy and ventricular arrhythmia**

	Baseline	Week 2	Month 6
Echocardiography( <i>n</i> = 52 )			
Left ventricular end-diastolic dimension( mm )	64 ± 1	64 ± 1	62 ± 2
Fractional shortening( % )	16 ± 1	19 ± 1*	18 ± 1**
Right heart catheterization( <i>n</i> = 17 )			
Cardiac index( l/min/m <sup>2</sup> )	2.79 ± 0.15	2.89 ± 0.19	
Pulmonary capillary wedge pressure( mmHg )	15 ± 2	12 ± 2 <sup>†</sup>	
Holter monitoring( <i>n</i> = 34 )			
Mean heart rate( beats/min )	73 ± 2	65 ± 2**	65 ± 2**
Premature ventricular complexes( /hr )	418 ± 184	122 ± 64**	45 ± 16**

Values are mean ± SE. <sup>†</sup>*p* < 0.10, \**p* < 0.05, \*\**p* < 0.01 compared with the baseline.

during amiodarone therapy in Japanese patients with idiopathic dilated cardiomyopathy and ventricular arrhythmia. Essentially, amiodarone has a negative inotropic effect and a potent vasodilatory effect<sup>1</sup>), so has complex effects on preload/afterload and heart rate, and improves the hemodynamics and ventricular contractility in patients with heart failure. Interestingly, the hemodynamic response to amiodarone seems to differ with the etiology of heart failure. Amiodarone tended to improve survival in patients with CHF-STAT and was associated with an increase in left ventricular ejection fraction in patients with nonischemic heart disease, but not ischemic heart disease<sup>16,17</sup>). Our results are similar to those of a placebo-controlled study, in which half of the patient population had idiopathic dilated cardiomyopathy and amiodarone was administered over 6 months<sup>5</sup>). The effect of amiodarone on left ventricular systolic function might not be simply due to the vasodilatory effect, with a slight increase in fractional shortening despite no change in left ventricular end-diastolic dimension. A direct inotropic effect with prolonged action potential duration through blocking of potassium channels or a marked reduction in frequency of ventricular arrhythmia might be partially responsible for the hemodynamic reaction to chronic amiodarone administration. However, the magnitude of this effect is unclear, because the change was quite small, and the pharmacological effects of amiodarone are multiple and complex.

Amiodarone produces direct depression of sinus and atrioventricular node automaticity and has a noncompetitive antiadrenergic action, which leads

to a reduced heart rate<sup>1,18</sup>). In our patients, amiodarone markedly reduced heart rate during ambulatory monitoring by week 2. However, 17 patients who underwent right heart catheterization did not show a subsequent decrease in cardiac index or an increased pulmonary capillary wedge pressure at week 2. Moreover, pulmonary capillary wedge pressure tended to decrease, although this did not reach statistical significance. Previous studies yielded conflicting results concerning these hemodynamic parameters<sup>4,6,7,19-21</sup>), possibly due to differences in several factors, such as left ventricular function, degree of heart failure, etiology, and dose and duration of administered amiodarone. In our patients who received amiodarone for over 2 weeks, the effects on cardiac index and pulmonary capillary wedge pressure might be partly due to the slight improvement in left ventricular systolic function.

This retrospective study consisted of small number of patients, without a control group. Moreover, left ventricular diastolic function using Doppler echocardiography could not be retrospectively evaluated because of technical factors. Therefore, this study is limited to a consideration of the hemodynamic effects of amiodarone in patients with idiopathic dilated cardiomyopathy. Most patients with symptomatic left ventricular systolic dysfunction should now be treated with an angiotensin converting enzyme inhibitor and a beta-blocker as first-line therapy<sup>22</sup>). Beta-blockers have major beneficial effects on left ventricular systolic function and symptomatic status in heart failure patients with or without amiodarone<sup>23</sup>). However, a role still

remains for amiodarone in the treatment of supraventricular and ventricular arrhythmia or prevention of sudden death in patients with nonischemic cardiomyopathy<sup>2,16,24</sup>). We consider that chronic amiodarone administration is useful as an adjunct to first-line therapy without worsening hemodynamics in Japanese patients with idiopathic dilated cardiomyopathy and ventricular arrhythmia.

## CONCLUSIONS

This study showed no worsening of the hemody-

namic state during chronic amiodarone administration in 52 Japanese patients with idiopathic dilated cardiomyopathy and ventricular arrhythmia, who were not taking beta-blockers or positive inotropic drugs. Although this study was retrospective, our results support the beneficial effect of amiodarone in Japanese patients with idiopathic dilated cardiomyopathy associated with high-risk arrhythmia.

## 要 約

### 特発性拡張型心筋症と心室不整脈を有する日本人患者における

#### アミオダロン慢性投与と血行動態: 後向き検討

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**目的:** 日本人においてアミオダロンによる不整脈治療の対象例は非虚血性心疾患、とくに特発性拡張型心筋症患者が主である。しかし、日本人の特発性拡張型心筋症患者についてアミオダロン治療による血行動態への効果を検討した報告は少ない。我々は心室不整脈を有する特発性拡張型心筋症患者についてアミオダロン慢性投与中の血行動態の変化を後向きに検討した。

**方 法:** 特発性拡張型心筋症(左室駆出率 $27 \pm 1\%$ )と心室頻脈性不整脈を有する52例(男性42例、女性10例、平均年齢 $53 \pm 2$ 歳)を対象とした。遮断薬や強心薬を併用している例は除外した。アミオダロン初期負荷として200-400 mg/dayを14日間、引き続き100-200 mg/dayを6ヵ月慢性投与した。心エコー図検査をアミオダロン開始前、開始後2週目と6ヵ月目に施行し、34例については同じ時期に24時間ホルター心電図検査も施行した。さらに17例についてはアミオダロン開始前と開始後2週目に右心カテーテル検査を施行した。計測値は平均 $\pm$ 標準誤差で示した。

**結 果:** 心エコー図検査による左室拡張末期径はアミオダロン開始前、投与中には有意な変化を認めず、左室内径短縮率は開始前 $16 \pm 1\%$ から投与開始後2週目 $19 \pm 1\%$ ( $p < 0.05$ )、6ヵ月目 $18 \pm 1\%$ ( $p < 0.01$ )と軽度ながら増加していた。ホルター心電図による平均心拍数および心室期外収縮数はアミオダロン開始後著明に減少していた。右心カテーテル検査による心係数はアミオダロン開始前後で変化を認めなかったが、肺動脈楔入圧は低下する傾向を認めた。

**結 論:** 今回の後向き検討から、特発性拡張型心筋症と心室不整脈を有する日本人患者において、アミオダロンを慢性投与しても血行動態は悪化しないことが示された。

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