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# Association of Electrocardiographic Variables and Effectiveness of Oral Amiodarone for Arrhythmia Management

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## ABSTRACT

**Background:** Oral amiodarone is used to manage refractory atrial and ventricular arrhythmias. Several studies have reported that assessment of serum amiodarone concentration is not associated with its effectiveness. In this study, we have attempted to identify electrocardiographic variables significantly associated with amiodarone effectiveness.

**Methods:** We analyzed data from 93 consecutive patients (72 men; mean age  $64.1 \pm 13.0$  years) who received oral amiodarone for the treatment of atrial fibrillation ( $n=50$ ), sustained ventricular tachycardia ( $n=44$ ), or ventricular fibrillation ( $n=20$ ). We assessed the relationships between amiodarone effectiveness and 12-lead electrocardiographic variables, particularly QT interval. The efficacy of amiodarone was evaluated by the improvement of tachyarrhythmia, change in the electrocardiograph and in the symptoms during follow-up period.

**Results:** During the administration period (mean duration  $31.8 \pm 26.0$  months), amiodarone was classified as effective, on the basis of maintenance of the sinus rhythm for 81 patients (87.1%); however, tachyarrhythmia remained in 12 patients (12.9%). Although amiodarone prolonged the QT interval, from  $411.0 \pm 52.5$  ms to  $457.6 \pm 59.0$  ms ( $P < 0.001$ ) during the loading phase, it did not change the interval during the maintenance phase even though the serum amiodarone concentration varied. Multivariate analysis revealed that the heart rate was the only variable associated with amiodarone effectiveness ( $67.4 \pm 12.9$  bpm in the effective group vs  $80.1 \pm 17.7$  bpm in the noneffective group,  $P=0.003$ ) one month after administration.

**Conclusions:** A decreased heart rate was significantly associated with amiodarone effectiveness; other electrocardiographic variables including QT/QTc interval, were not associated with its effectiveness.

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**KEYWORDS:** atrial fibrillation, ventricular tachycardia, ventricular fibrillation, QT interval, RR interval

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## Introduction

Amiodarone is classified as a class III antiarrhythmic drug in the Vaughan-Williams classification. The Sicilian Gambit classification describes many pharmacological effects of amiodarone. In addition to its potassium channel blocking effect, it is a calcium channel blocker, sodium channel blocker, and has sympathetic inhibitory action. Furthermore, it has a long half-life due to its extensive distribution in fatty tissue. Oral amiodarone is effective for treating refractory atrial and ventricular tachyarrhythmia.<sup>1-6)</sup>

The antiarrhythmic and pharmacological effects of amiodarone have been reported.<sup>7-10)</sup> Several studies have reported that assessment of serum amiodarone concentration is not associated with its effectiveness. On the other hand, association in short-term administration between the antiarrhythmic effects and electrocardiographic variables, especially QT interval were well reported.

However, the correlations of long-term administration of amiodarone with changes in electrocardiographic variables and antiarrhythmic effects are not well understood. Amiodarone is a potassium channel blocker and it decreases  $I_{Ks}$  currents. Decreasing the  $I_{Ks}$  currents prolongs the QT interval and develops the tachy-arrhythmias effect.

In this study, we attempted to identify the transition of electrocardiographic variables including QT interval that were significantly associated with amiodarone effectiveness during therapy. In addition, the development of the efficacy of oral amiodarone is a time consuming process. We analyzed the serial change of electrocardiographic variables and examined whether which factors predict the effectiveness of amiodarone at an early stage.

## Methods

### Study population

In this retrospective study, we reviewed the records of 191 consecutive patients who received oral amiodarone to inhibit atrial or ventricular arrhythmias at our center between January 2008 and December 2013. The study protocol was approved by the ethics committee of Toho University Omori Medical Center with number 26-302.

The patients who could not be followed with 12-lead electrocardiographic variables were excluded. Following exclusion, the total number of patients assessed was 93. The effectiveness of amiodarone was investigated during

a mean (SD) follow-up period of 31.8 (26.0) months, and the correlations of amiodarone effectiveness with 12-lead electrocardiographic variables including QT interval were assessed.

### Amiodarone administration protocol

Amiodarone was administered during loading and maintenance dose phases. During the loading phase, amiodarone was started at 400 mg daily orally or 750 mg daily intravenously and was continued at a dose of 50-400 mg daily after the initial loading phase, one-two weeks. The dose was determined on the basis of arrhythmia control and on the development of side effects. In this study, one month following the initial amiodarone therapy has been defined as the maintenance phase.

During the maintenance phase, the presence of symptoms was evaluated, and physical examinations, 12-lead electrocardiography and blood testing were conducted every 1-3 months. Plasma concentrations of amiodarone and the metabolites of amiodarone (M-amiodarone) were measured every 3-6 months.

### Effect of amiodarone therapy

The efficacy of amiodarone was evaluated by the improvement in tachyarrhythmia, the change in electrocardiograph and the symptoms during follow-up period. If patients had symptoms, 24-hr Holter monitoring was conducted. In patients with an implanted pacemaker or implantable cardioverter defibrillator, the absence of arrhythmia was defined as no episode of arrhythmia recorded by these devices.

We divided the 93 consecutive patients into two groups: the "effective group" and "noneffective group." The "effective group" was defined as the group in which tachyarrhythmia, atrial fibrillation (AF), sustained ventricular tachycardia (VT), and ventricular fibrillation (VF) had resolved.

### Follow-up of amiodarone side effects

To prevent side effects such as pulmonary toxicity, thyroid dysfunction, and hepatic disorders, standard blood tests, including serum thyroid-stimulating hormone, free-T3, free-T4, and serum KL-6 level, were checked every 3-6 months during amiodarone therapy. A chest radiograph was obtained every 3 months. Detection of these side effects during follow-up resulted in the cessation or in the adjustment of amiodarone therapy.

### Assessment of electrocardiographic variables

An electrocardiography device (Nihon Kohden, Tokyo, Japan) was used to record 12-lead electrocardiograms.

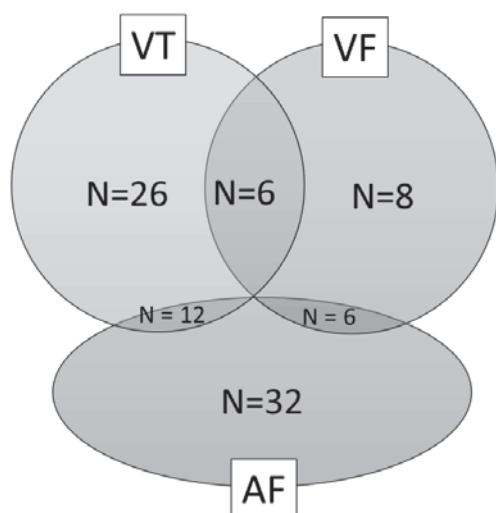


Fig. 1 Distribution of the patients with atrial fibrillation (AF), ventricular tachycardia (VT) and ventricular fibrillation (VF).

Heart rate, PQ, QRS, and QT interval were measured automatically as part of the test. However, we visually confirmed that the variables measured automatically were correct. QT interval was measured from onset of the QRS complex to the end of the T wave. When a U wave was present, the QT interval was measured to the nadir of the curve between the T and U wave. Bazett's formula,  $QTc = QT / (RR)^{1/2}$ , was used to calculate QTc interval from the QT interval.

Electrocardiography was performed before amiodarone therapy and at 1 and 6 months after the start of amiodarone therapy. Data for the variables of interest were then compared between the effective group and the noneffective group.

#### Statistical analysis

All continuous data are expressed as means  $\pm$  standard deviation, medians (interquartile range), or numbers (%). Univariate analysis (the unpaired t-test and Fisher exact test) was used for comparisons between groups. Two-way repeated measures analysis of variance was used to analyze changes in electrocardiographic variables at baseline, 1 and 6 months. Logistic regression was used for multivariate analysis. A P value of  $<0.05$  was considered to indicate statistical significance. All statistical analyses were performed using the software package R commander version 1.24.<sup>11)</sup>

#### Ethical considerations

This study was approved by our institutional review board (number 26-302). All patients gave their informed

consent for the study protocol, which was approved by the institutional review board. All private patient data were anonymized before analysis in this study.

## Results

### Baseline characteristics

The mean age was  $64.1 \pm 13.0$  years, 72 (77.4%) of the patients were men, and the mean body mass index was  $23.1 \pm 4.7$  kg/m<sup>2</sup>. Among the 93 consecutive patients, amiodarone was used to treat AF (n=50; 53.8%), VT (n=44; 47.3%), or VF (n=20; 21.5%), and the others (n=3; 3.2%). Fig. 1 shows the distribution of AF, VT and VF. The mean amiodarone dose was  $152.2 \pm 62.9$  mg, and the mean duration of administration was  $31.8 \pm 26.0$  months. During the median follow-up period, which was 1270 days (quartiles 1 to 3,757 to 1900 days), amiodarone effectiveness was determined in 81 patients (87.1%). Six patients were treated with other antiarrhythmic drugs, and 68 patients (73.1%) received beta blockers.

Table 1, 2 show the baseline characteristics of the study groups. There were significantly more AF patients in the noneffective group than in the effective group: 10 (83.3%) vs. 40 (49.4%), respectively ( $P=0.03$ ). However, there were no significant differences in the VT/VF patients between the effective group and the noneffective group. The maintenance dose of amiodarone was not significantly higher in the effective group as compared to the noneffective group:  $154.6 \pm 65.0$  mg vs  $150.0 \pm 63.3$  mg. There was no significant difference between groups in the use of beta blockers or other antiarrhythmic drugs. On the other hand, between the patients with and without AF, there were no significant differences in the clinical factors except for LVDD (Table 2).

Of the 93 patients, side effects were seen in 23 patients (24.5%). Interstitial pneumonia was seen in 4 patients, thyrotoxicosis in 13, drug eruptions in bradycardia in one, a prolonged QT in one. In the 23 patients who developed the side effects, amiodarone therapy was stopped in the 13 patients (56.5%).

### Electrocardiography variables and amiodarone

Changes in electrocardiographic variables are shown in Fig. 2. Amiodarone led to a significant increase in the QT interval and a decrease in heart rate during follow-up. Amiodarone prolonged the QT interval during the loading phase, from  $411.0 \pm 52.5$  ms at baseline to  $432.7 \pm 46.1$  ms at one month ( $P<0.001$ ), farther during the maintenance phase, QT interval was prolonged, from  $432.7 \pm 46.1$  ms at

Table 1 Patient characteristics at baseline

|                                | Over all<br>(93) | Non-Effective group<br>(12) | Effective group<br>(81) | P     |
|--------------------------------|------------------|-----------------------------|-------------------------|-------|
| Male (%)                       | 72 (77.4)        | 10 (83.3)                   | 62 (76.5)               | 0.728 |
| Age (years)                    | 64.1 ± 13.0      | 68.1 ± 8.2                  | 63.5 ± 13.5             | 0.251 |
| Height (cm)                    | 163.5 ± 9.6      | 163.8 ± 9.2                 | 163.4 ± 9.7             | 0.891 |
| Weight (Kg)                    | 62.4 ± 16.2      | 62.8 ± 8.8                  | 62.4 ± 17.1             | 0.925 |
| BMI (kg/m <sup>2</sup> )       | 23.1 ± 4.7       | 23.2 ± 3.7                  | 23.1 ± 4.9              | 0.955 |
| Medical history                |                  |                             |                         |       |
| DM                             | 28 (30.1)        | 4 (33.3)                    | 24 (29.6)               | 0.749 |
| HT                             | 44 (47.3)        | 8 (66.7)                    | 36 (44.4)               | 0.217 |
| CHF                            | 59 (63.4)        | 7 (58.3)                    | 52 (64.2)               | 0.753 |
| IHD                            | 44 (47.3)        | 4 (33.3)                    | 40 (49.4)               | 0.364 |
| DL                             | 33 (35.5)        | 3 (25.0)                    | 30 (37.0)               | 0.529 |
| HD                             | 6 (6.5)          | 0 (0.0)                     | 6 (7.4)                 | 0.999 |
| AF (%)                         | 50 (53.8)        | 10 (83.3)                   | 40 (49.4)               | 0.033 |
| VT (%)                         | 44 (47.3)        | 3 (25.0)                    | 41 (50.6)               | 0.127 |
| VF (%)                         | 20 (21.5)        | 1 (8.3)                     | 19 (23.5)               | 0.451 |
| Maintain dose of AMD (mg)      | 152.2 ± 62.9     | 154.6 ± 65.0                | 150.0 ± 63.3            | 0.840 |
| Concentration of AMD (µg/ml)   | 0.86 ± 0.43      | 0.89 ± 0.35                 | 0.85 ± 0.44             | 0.096 |
| Concentration of M-AMD (µg/ml) | 0.65 ± 0.31      | 0.70 ± 0.24                 | 0.64 ± 0.32             | 0.607 |
| BB                             | 68 (73.1)        | 9 (75.0)                    | 59 (72.8)               | 0.999 |
| CCB                            | 14 (15.1)        | 10 (83.3)                   | 69 (85.2)               | 0.999 |
| Diuretics                      | 32 (34.4)        | 4 (33.3)                    | 28 (34.6)               | 0.999 |
| ARB, ACEI                      | 58 (62.4)        | 6 (50.0)                    | 52 (64.2)               | 0.451 |
| Echocardiography               |                  |                             |                         |       |
| EF (%)                         | 47.7 ± 19.0      | 53.4 ± 16.5                 | 46.8 ± 19.3             | 0.267 |
| LVDd (mm)                      | 57.5 ± 12.1      | 57.4 ± 10.4                 | 57.5 ± 12.4             | 0.982 |
| LAD (mm)                       | 45.1 ± 9.0       | 46.0 ± 4.6                  | 44.8 ± 9.6              | 0.690 |
| Laboratory data                |                  |                             |                         |       |
| Cr (mg/dl)                     | 1.38 ± 1.51      | 1.05 ± 0.35                 | 1.42 ± 1.61             | 0.427 |
| eGFR (ml/min)                  | 57.3 ± 24.8      | 57.3 ± 16.3                 | 57.3 ± 25.9             | 0.996 |
| Hb (g/dl)                      | 13.3 ± 2.0       | 13.7 ± 1.4                  | 13.3 ± 2.1              | 0.472 |
| BNP (pg/ml)                    | 507.9 ± 556.5    | 246.2 ± 132.1               | 546.3 ± 583.9           | 0.096 |
| HbA1c (%)                      | 5.8 ± 0.8        | 5.9 ± 0.5                   | 5.8 ± 0.8               | 0.771 |
| TSH (µIU/ml)                   | 4.9 ± 22.5       | 4.3 ± 2.4                   | 5.0 ± 23.7              | 0.931 |
| f-T3 (pg/ml)                   | 2.37 ± 0.67      | 2.28 ± 0.78                 | 2.38 ± 0.66             | 0.684 |
| f-T4 (ng/ml)                   | 1.46 ± 0.61      | 1.60 ± 0.33                 | 1.44 ± 0.64             | 0.490 |

BMI, body mass index; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; AMD, amiodarone; M-AMD, metabolites of amiodarone; AADs, antiarrhythmic drugs; BB; beta blocker, CCB, calcium channel blocker; ARB/ACEI, angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor; DM, diabetes mellitus; HT, hypertension; CHF, congestive heart failure; IHD, ischemic heart disease; DL, dyslipidemia; HD, hemodialysis; EF, ejection fraction; LAD, left atrial diameter; LVDd, left ventricular diameter (diastolic); eGFR, estimated glomerular filtration

Data are expressed as mean ± SD or number (%). P values were calculated by using the unpaired t-test and Fisher exact test.

one month to 452.1 ± 53.7 ms at six months ( $P=0.001$ ). Amiodarone therapy did not increase the QTc interval, from 454.5 ± 56.5 ms to 457.6 ± 59.0 ms ( $P=0.69$ ). The QRS interval did not significantly change before or after the start of amiodarone therapy.

Analysis of the correlation between electrocar-

diographic variables and amiodarone effectiveness showed no significant difference between the effective and non-effective groups in any variable at baseline. Heart rate was significantly lower after amiodarone therapy. In particular, heart rate at 1 month after amiodarone therapy was lower in the effective group as compared to that in the noneffec-

Table 2 Patient characteristics between with and without AF patients

|                          | The others<br>(43) | AF<br>(50)    | P      |
|--------------------------|--------------------|---------------|--------|
| Male (%)                 | 35 (81.4)          | 37 (74.0)     | 0.461  |
| Age (years)              | 62.7 ± 11.8        | 65.2 ± 13.9   | 0.353  |
| Height (cm)              | 163.6 ± 9.3        | 163.3 ± 1.0   | 0.884  |
| Weight (Kg)              | 64.1 ± 16.3        | 61.0 ± 16.2   | 0.354  |
| BMI (kg/m <sup>2</sup> ) | 23.7 ± 4.9         | 22.7 ± 4.6    | 0.328  |
| Medical history          |                    |               |        |
| DM                       | 14 (32.6)          | 14 (28.0)     | 0.657  |
| HT                       | 18 (41.9)          | 26 (52.0)     | 0.406  |
| CHF                      | 26 (60.5)          | 33 (66.0)     | 0.667  |
| IHD                      | 25 (58.1)          | 19 (38.0)     | 0.063  |
| DL                       | 19 (44.2)          | 14 (28.0)     | 0.130  |
| BB                       | 34 (79.1)          | 34 (68.0)     | 0.251  |
| Diiuretics               | 14 (32.6)          | 18 (36.0)     | 0.828  |
| ARB, ACEI                | 32 (74.4)          | 26 (52.0)     | 0.033  |
| Echocardiography         |                    |               |        |
| EF (%)                   | 43.9 ± 18.6        | 50.9 ± 19.0   | 0.086  |
| LVDd (mm)                | 6.2 ± 1.2          | 5.3 ± 1.1     | <0.001 |
| LAD (mm)                 | 4.4 ± 1.0          | 4.6 ± 0.8     | 0.626  |
| Laboratory data          |                    |               |        |
| Cr (mg/dl)               | 1.5 ± 1.3          | 1.3 ± 1.7     | 0.644  |
| eGFR (ml/min)            | 54.2 ± 22.9        | 60.1 ± 26.3   | 0.260  |
| BNP (pg/ml)              | 474.0 ± 503.0      | 540.3 ± 607.3 | 0.579  |

BMI, body mass index; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; BB, beta blocker, ARB/ACEI, angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor; DM, diabetes mellitus; HT, hypertension; CHF, congestive heart failure; IHD, ischemic heart disease; DL, dyslipidemia; EF, ejection fraction; LAD, left atrial diameter; LVDd, left ventricular diameter (diastolic); eGFR, estimated glomerular filtration

Data are expressed as mean ± SD or number (%) . P values were calculated by using the unpaired t-test and Fisher exact test.

tive group (67.4 ± 12.9 bpm vs 80.1 ± 17.7 bpm, respectively;  $P=0.003$ ; Table 3 and Fig. 2).

We set the cut-off value of the heart rate to 75 bpm, because an ROC curve comparing the heart rate and the efficacy of amiodarone showed the cut-off value of the heart rate to be 75 bpm (AUC, 0.71; 95% CI, 0.552-0.875, Fig. 3). Among clinical factors, logistic regression models from multivariate analysis revealed that a decreased heart rate <75 bpm was the only variable associated with amiodarone effectiveness (OR 0.22, 95% CI 0.057-0.87,  $P=0.03$ ; Table 4), after adjusting for arrhythmia type. We decided a cut-off value of the QT interval of 430 ms, because the mean of QT interval was about 430 ms.

## Discussion

Amiodarone prolonged the QT interval and decreased the heart rate. QT and QTc interval did not predict the effectiveness of amiodarone. Multivariate analysis revealed that a decreased heart rate was the only variable associated with amiodarone effectiveness. Fortunately, the heart rate is easily monitored and might thus be a useful marker of amiodarone effectiveness.

### Pharmacological effects of amiodarone

Amiodarone is classified as a class III antiarrhythmic drug according to the Vaughan-Williams classification. The electrophysiological effects of amiodarone are complex because it has the effects of a potassium channel blocker, a calcium channel blocker, a sodium channel blocker, and a sympathetic inhibitory action. Furthermore, chronic amiodarone effects develop in the maintenance phase, while acute administration affects the loading phase.<sup>12)</sup> There were some reports that the follow-up period was one month or more after initial administration of amiodarone.<sup>2,13)</sup> And the chronic effect of amiodarone is developed to change its pharmacologic effects at 4 weeks after initiation of amiodarone therapy.<sup>7)</sup> According these reports, the maintenance phase was defined as one month after initial amiodarone therapy.

Previous reports show that acute administration of amiodarone inhibits  $I_{Na}$ ,  $I_{CaL}$ ,  $I_{Kr}$ ,  $I_{K1}$ ,  $I_f$ ,  $I_{KACH}$ , and  $I_{KATP}$  currents,<sup>7,13)</sup> while chronic administration inhibits  $I_{Ks}$  and  $I_{to}$  currents.<sup>1,2,7,13)</sup> Action potential duration is not prolonged during acute administration, regardless of inhibition of the  $I_K$  currents, because inhibition of the inward  $Na^+$  and  $Ca^{2+}$  currents is greater than inhibition of the outward  $K^+$  current during acute amiodarone administration.<sup>7,14,15)</sup> During chronic administration, the inhibitory action of amiodarone on  $I_K$ s and  $I_{to}$  currents prolongs the action potential duration, which suppresses VT/VF.<sup>1,3,15,16)</sup>

### Electrocardiographic variables and amiodarone effectiveness

Amiodarone prolonged the RR interval but not the QT/QTc interval during the acute phase. However, chronic amiodarone administration prolonged the QT and QTc intervals. Prolongation of amiodarone-induced repolarization is homogeneous; therefore, the risk of Torsade de Pointes due to amiodarone-induced QT prolongation is lower than that with other antiarrhythmic drugs.<sup>1,3)</sup>

Some previous studies have reported an association between the amiodarone effectiveness and the QT inter-



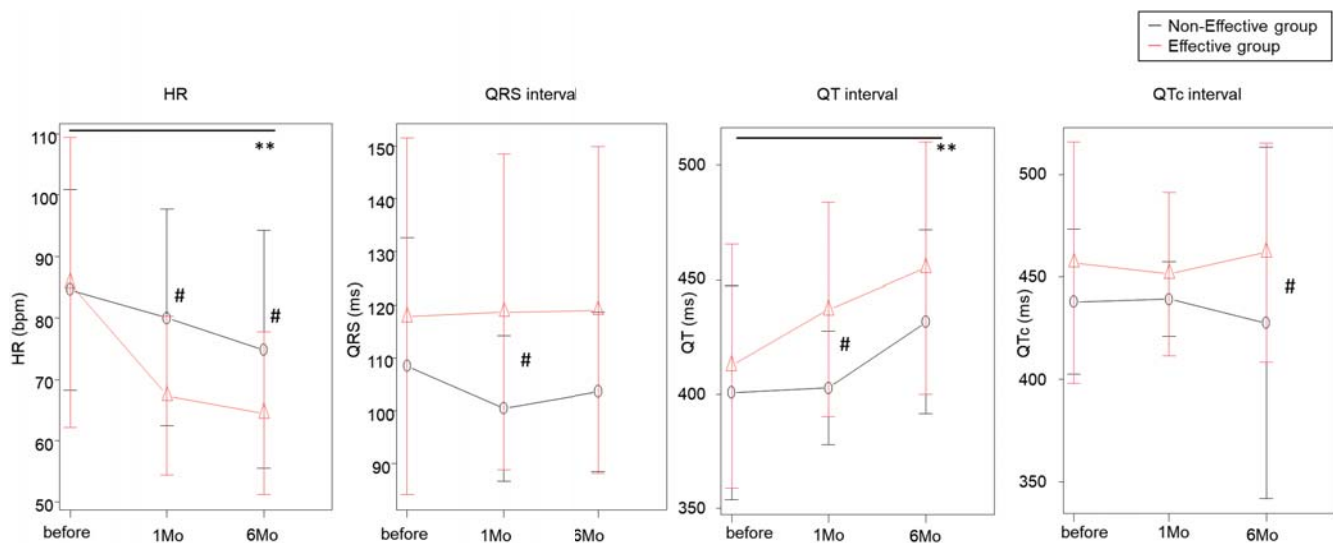


Fig. 2 Change in electrocardiographic variables

Amiodarone significantly increased the QT interval and decreased the heart rate during follow-up. P values were calculated by two-way repeated-measures ANOVA. Error bars showed standard deviation.

\*  $P < 0.05$ , \*\*  $P < 0.001$  for intragroup differences; #  $P < 0.05$  for differences between groups

Table 3 Electrocardiographic variables at baseline and 1 month after amiodarone therapy

|                              | Non-Effective group<br>(12) | Effective group<br>(81) | P     |
|------------------------------|-----------------------------|-------------------------|-------|
| Electrocardiography baseline |                             |                         |       |
| HR (bpm)                     | 84.6 ± 16.4                 | 85.7 ± 23.6             | 0.870 |
| PQ (ms)                      | 204.0 ± 50.2                | 181.9 ± 50.8            | 0.403 |
| QRS (ms)                     | 108.5 ± 24.2                | 117.8 ± 33.7            | 0.358 |
| QT (ms)                      | 400.8 ± 46.9                | 412.5 ± 53.4            | 0.471 |
| QTc (ms)                     | 437.9 ± 35.4                | 457.0 ± 58.8            | 0.277 |
| Electrocardiography 1 Mo     |                             |                         |       |
| HR_1Mo (bpm)                 | 80.1 ± 17.7                 | 67.4 ± 12.9             | 0.003 |
| PQ_1Mo (ms)                  | 203.0 ± 39.7                | 1991.8 ± 46.6           | 0.569 |
| QRS_1Mo (ms)                 | 100.5 ± 13.8                | 118.8 ± 29.9            | 0.040 |
| QT_1Mo (ms)                  | 402.8 ± 24.8                | 437.1 ± 47.0            | 0.015 |
| QTc_1Mo (ms)                 | 439.3 ± 18.1                | 451.5 ± 40.0            | 0.301 |

Mo, month; HR, heart rate

Data are expressed as mean ± SD or number (%). P values were calculated by using the unpaired t-test.

val.<sup>1-3)</sup> In addition, some reports found that amiodarone-induced QT interval prolongation was related to the drug concentration.<sup>2)</sup> However, these studies reported no significant correlation between amiodarone effectiveness and the 12-lead electrocardiography variables, including QT interval.<sup>2)</sup> QT interval was prolonged at one and six months after amiodarone therapy. In addition, PQ and QRS interval were unchanged, as was the case in previous reports.<sup>17)</sup>

#### Heart rate and amiodarone effectiveness

Among the clinical variables investigated, only a de-

creased heart rate was associated with amiodarone effectiveness. Heart rate at 12 months after amiodarone therapy did not significantly differ between the effective and noneffective group ( $64.0 \pm 10.6$  vs.  $66.3 \pm 14.3$  bpm,  $P=0.70$ ); however, a few patients ( $n=4$ ) in the noneffective group received amiodarone at 12 months after therapy, which might explain the nonsignificant difference between groups.

Amiodarone blocks the Na and HCN channels during acute administration. Prolongation of action potential by

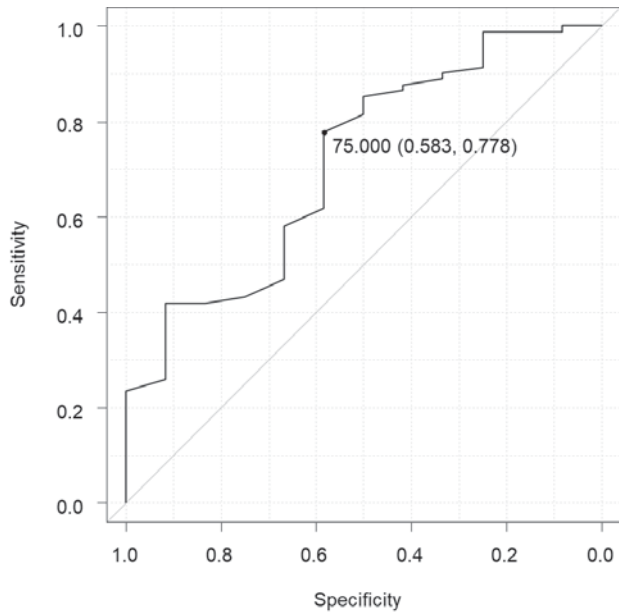


Fig. 3 ROC Curves between the heart rate at one month and efficacy of amiodarone

An ROC curve comparing the heart rate and efficacy shows that the cut-off value of the heart rate was 75 (AUC, 0.71; 95% CI, 0.552-0.875).

inhibiting  $I_{Ks}$  current and alpha- or beta-blocking activity occurs during chronic administration. Sinus node automaticity and suppression of intraventricular conduction due to blocking of the Na and HCN channels also occur during the acute phase, and the heart rate is decreased by these processes. The action potential duration and QT interval are prolonged during chronic administration, and tachyarrhythmias such as VT/VF and AF are suppressed.<sup>1,2,7,13</sup> These previous findings suggest how a decreased heart rate might function as an early marker of amiodarone effectiveness.

Tachyarrhythmias are suppressed by not only K channel blocking, but also by Na, HCN channel receptor blocking activity. Prolongation of amiodarone-induced repolarization is homogeneous. Therefore, QT interval may not be associated with amiodarone effectiveness. Reduction of heart rate decreases the risk of arrhythmia development due to the multichannel blocking action of amiodarone. These channel blocking effects inhibit delayed afterdepolarization and Ca spark. These blocking effects also lead to the reduction of heart rate.  $I_{Ks}$  and  $I_{to}$  currents were firmly suppressed similarly to other channel currents in patients with decreased heart rate, and it seems that antiarrhythmic effect was obtained. The other class III antiarrhythmia drugs such as nifekalant, have the reverse use-

Table 4 Predictors of amiodarone effectiveness, as determined by multivariate logistic analysis

| N = 93       | Multivariable Analysis |         |
|--------------|------------------------|---------|
|              | OR (95%CI)             | P value |
| HR_1Mo < 75  | 0.22 (0.057-0.865)     | 0.030   |
| QT_1Mo > 430 | 0.66 (0.100-4.340)     | 0.665   |
| AF           | 3.03 (0.642-14.300)    | 0.161   |
| VT           | 0.68 (0.125-3.710)     | 0.658   |
| VF           | 0.61 (0.097-3.790)     | 0.592   |

OR, odds ratio; CI, confidence interval; Mo, month; HR, heart rate; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation

P values were determined by multivariate logistic analysis.

dependence of the  $K^+$  channel blocking action. However, amiodarone does not have the reverse use-dependence action. Therefore, bradycardia might not increase the effect of amiodarone, instead amiodarone effects may induce bradycardia.

Heart rate is also affected by other drugs, such as calcium channel blockers and beta blockers. However, in the present study there was no significant difference in the use of these drugs between groups.

#### Thyroid effect and amiodarone

Amiodarone-induced thyrotoxicosis has been reported. Amiodarone inhibits conversion of the enzyme triiodothyronine to thyroxine in peripheral tissues. Amiodarone contains iodine, an excess of which suppresses the synthesis and secretion of thyroid hormone (Wolff-Chaikoff effect).<sup>18,19</sup> Amiodarone-induced hyperthyroidism is a destructive form of thyroiditis. However, the amiodarone dose is not correlated with hyperthyroidism risk. If hyperthyroidism develops, it usually resolves within a few months.<sup>19</sup>

Previous studies showed phenotypic resemblance between long-term amiodarone therapy and amiodarone-induced hypothyroidism. The factors noted in this resemblance were prolongation of the action potential duration and refractory period, decreased heart rate, and decreased myocardial oxygen consumption. However, some reports have proposed different hypotheses.<sup>14,20</sup>

In the present study, hypothyroidism was present in 11 patients (11.8%). Although serum thyroid-stimulating hormone concentration was significantly higher after amiodarone therapy, it was not significantly correlated with amiodarone effectiveness, heart rate, or thyroid function.



### Study limitations

This study had some potential limitations. First, it was a retrospective, observational study at a single center. Second, there were only a few cases of the noneffective group of VT/VF, when patients were divided into 2 groups (VT/VF and AF), and it might make it a poor analysis. On the other hand, we tried addressing this problem to use the logistic regression model after adjusting for this factor, because there were no significant differences in the patients who developed VT/VF and AF (Table 2).

Finally, only a few patients received amiodarone for longer than six months, which might have resulted in bias. Larger-scale studies are therefore necessary to confirm our conclusions.

### Conclusions

Decreased heart rate < 75 bpm at one month after amiodarone therapy was the only predictor associated with amiodarone effectiveness. Serum amiodarone concentration and other electrocardiographic variables, including QT interval, were not predictors associated with amiodarone effectiveness.

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### References

- 1) Meierhenrich R, Helguera ME, Kidwell GA, Tebbe U. Influence of amiodarone on QT dispersion in patients with life-threatening ventricular arrhythmias and clinical outcome. *Int J Cardiol.* 1997; 60: 289-94.
- 2) Aiba T, Shimizu W, Inagaki M, Satomi K, Taguchi A, Kurita T, et al. Excessive increase in QT interval and dispersion of repolarization predict recurrent ventricular tachyarrhythmia after amiodarone. *Pacing Clin Electrophysiol.* 2004; 27: 901-9.
- 3) Nafrialdi N, Kurniawan TG, Setiawati A, Makmun LH. QT interval prolongation associated with amiodarone use in Cipto Mangunkusumo Hospital, Jakarta. *Acta Med Indones.* 2014; 46: 292-7.
- 4) Grimm W, Steder U, Menz V, Hoffmann J, Maisch B. Effect of amiodarone on QT dispersion in the 12-lead standard electrocardiogram and its significance for subsequent arrhythmic events. *Clin Cardiol.* 1997; 20: 107-10.
- 5) Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol.* 2003; 41: 255-62.
- 6) Van Herendael H, Dorian P. Amiodarone for the treatment and prevention of ventricular fibrillation and ventricular tachycardia. *Vasc Health Risk Manag.* 2010; 6: 465-72.
- 7) Kodama I, Kamiya K, Toyama J. Cellular electropharmacology of amiodarone. *Cardiovasc Res.* 1997; 35: 13-29.
- 8) Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation.* 1998; 98: 2574-9.
- 9) Kowey PR, Friehling TD, Marinchak RA, Sulpizi AM, Stohler JL. Safety and efficacy of amiodarone. The low-dose perspective. *Chest.* 1988; 93: 54-9.
- 10) Mattioni TA, Zheutlin TA, Sarmiento JJ, Parker M, Lesch M, Kehoe RF. amiodarone in patients with previous drug-mediated torsade de pointes. Long-term safety and efficacy. *Ann Intern Med.* 1989; 111: 574-80.
- 11) Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant.* 2013; 48: 452-8.
- 12) Koike H, Fujino T, Koike M, Shinohara M, Kitahara K, Kinoshita T, et al. Obesity is associated with the development of interstitial pneumonia under long-term administration of amiodarone in refractory atrial fibrillation patients. *Int Heart J.* 2016; 57: 30-4.
- 13) Komatsu T, Tachibana H, Sato Y, Ozawa M, Kunugita F, Nakamura M. Long-term efficacy of amiodarone therapy for the prevention of recurrence of paroxysmal atrial fibrillation. Analysis based on patient characteristics. *Int Heart J.* 2011; 52: 212-7.
- 14) Kodama I, Kamiya K, Toyama J. amiodarone: ionic and cellular mechanisms of action of the most promising class III agent. *Am J Cardiol.* 1999; 84: 20-8.
- 15) Kamiya K, Nishiyama A, Yasui K, Hojo M, Sanguinetti MC, Kodama I. Short- and long-term effects of amiodarone on the two components of cardiac delayed rectifier K(+) current. *Circulation.* 2001; 103: 1317-24.
- 16) Varro A, Virag L, Papp JG. Comparison of the chronic and acute effects of amiodarone on the calcium and potassium currents in rabbit isolated cardiac myocytes. *Br J Pharmacol.* 1996; 117: 1181-6.
- 17) Kuga K, Yamaguchi I, Sugishita Y. Effect of intravenous amiodarone on electrophysiologic variables and on the modes of termination of atrioventricular reciprocating tachycardia in Wolff-Parkinson-White syndrome. *Jpn Circ J.* 1999; 63: 189-95.
- 18) Sato K, Miyakawa M, Eto M, Inaba T, Matsuda N, Shiga T, et al. Clinical characteristics of amiodarone-induced thyrotoxicosis and hypothyroidism in Japan. *Endocr J.* 1999; 46: 443-51.
- 19) Jabrocka-Hybel A, Bednarczuk T, Bartalena L, Pach D, Ruchala M, Kaminski G, et al. amiodarone and the thyroid. *Endokrynol Pol.* 2015; 66: 176-86.
- 20) Drvota V, Bronnegard M, Haggblad J, Barkhem T, Sylven C. Downregulation of thyroid hormone receptor subtype mRNA levels by amiodarone during catecholamine stress in vitro. *Biochem Biophys Res Commun.* 1995; 211: 991-6.