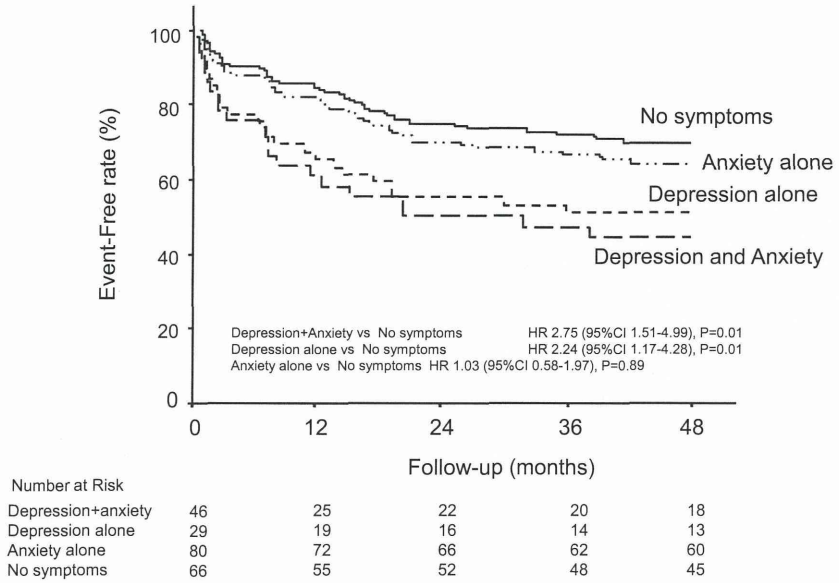


Number at Risk					
Depression+anxiety	46	25	22	20	18
Depression alone	29	19	16	14	13
Anxiety alone	80	72	66	62	60
No symptoms	66	55	52	48	45

Fig. 2. Kaplan–Meier curve for the primary outcome (death from any cause or rehospitalization due to worsened heart failure or refractory arrhythmia) in the four heart failure patient groups on the basis of depression and anxiety. HR, hazard ratio; CI, confidence interval.

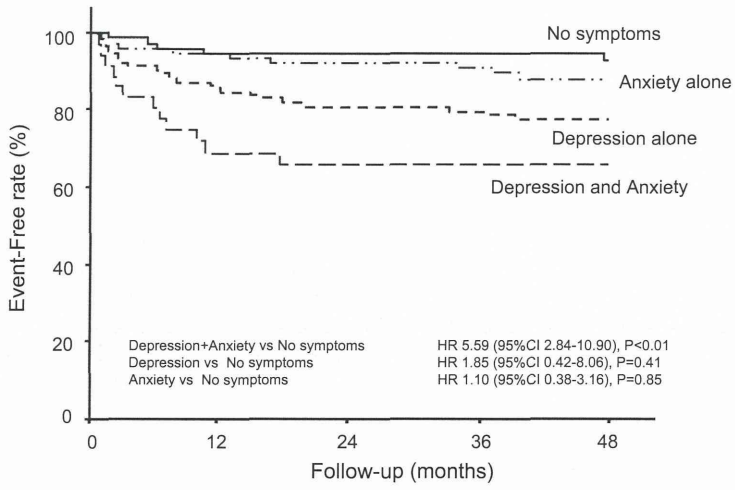
Table 2
Causes of death and rehospitalization for cardiac events.

	Depression alone ($n=29$)	Anxiety alone ($n=80$)	Depression + anxiety ($n=46$)	No symptoms ($n=66$)	p value
Death from any cause	8(28%)	4(5%)	17(37%)	2(3%)	<0.01
Cardiac death	8(28%)	4(5%)	16(35%)	2(3%)	<0.01
Sudden death	2(7%)	1(1%)	1(2%)	0(0%)	0.96
Heart failure	6(21%)	3(4%)	15(33%)	2(3%)	<0.01
Non-cardiac death	0(0%)	0(0%)	1(2%)	0(0%)	0.06
Hospitalization for heart failure	7(24%)	15(19%)	5(11%)	4(6%)	0.90
Hospitalization for refractory arrhythmia	3(10%)	2(3%)	1(2%)	1(2%)	0.29

Values are n (%).

from any cause (HR 5.59, 95% CI: 2.84–10.90, $p < 0.01$) compared to patients with no symptoms.

The univariate analysis showed that in addition to NYHA functional class, implantation of an ICD/CRT-D, LVEF ≤35%, BNP at discharge >250 pg/ml, eGFR <60 ml/min/1.73 m^2, depression alone, and a combination of depression and anxiety, but not anxiety alone, were significant predictors for the primary outcome (Table 3).



Number at Risk					
Depression+anxiety	46	31	29	29	29
Depression alone	29	24	22	21	20
Anxiety alone	80	71	64	60	60
No symptoms	66	56	55	55	53

Fig. 3. Kaplan–Meier curve for death from any cause in the four heart failure patient groups on the basis of depression and anxiety. HR, hazard ratio; CI, confidence interval.

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Table 3
Univariate predictors for the primary outcome.

	Hazard ratio (95% CI)	*p* value
Female gender	0.70 (0.43–1.15)	0.16
Age ≥65 years	0.89 (0.56–1.42)	0.64
NYHA functional class at discharge	3.97 (2.61–6.04)	<0.01
Implantation of an ICD/CRT-D	4.26 (2.56–7.07)	<0.01
eGFR <60 ml/min/1.73 m^2	2.88 (1.81–4.59)	<0.01
BNP at discharge >250 pg/ml	2.95 (1.80–4.81)	<0.01
LVEF ≤35%	1.99 (1.24–3.19)	<0.01
Depression	2.59 (1.56–4.20)	<0.01
Anxiety	1.71 (0.98–2.98)	0.05
Depression and anxiety	2.63 (1.56–4.41)	<0.01

BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy with a defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 4
Relationship of depression and anxiety with the primary outcome after adjusting for age, gender, New York Heart Association class, device implantation, estimated glomerular filtration rate, B-type natriuretic peptide, and left ventricular ejection fraction.

	Hazard ratio (95% CI)	*p* value
Depression	1.69 (0.97–2.95)	0.06
Anxiety	1.46 (0.80–2.65)	0.21
Depression and anxiety	1.96 (1.00–3.27)	0.04

The relationship between depression and anxiety with the primary outcome after adjusting for age, gender, NYHA class, device implantation, eGFR, BNP, and LVEF revealed that patients with clustered depression and anxiety had an increased risk of the primary outcome, but depression alone was not related to the primary outcome (Table 4).

Discussion

Our study revealed that the prevalence of clustered depression and anxiety was 20% in hospitalized patients with HF. Furthermore, we found that patients with both depression and anxiety were at an increased risk of the primary composite outcome: death from any cause and rehospitalization due to worsened HF and refractory arrhythmia. Finally, clustered depression and anxiety, but not depression or anxiety alone, were shown to be independent factors associated with worsening clinical outcomes.

Several studies have shown that depression is an independent predictor of mortality in patients with HF [1–13]. In our study, depression was a risk factor in the univariate analysis but was not an independent factor after adjusting for clinical variables at discharge related to the primary outcome. There are a number of possible reasons for the differences in our results compared with those in the previous reports. First, our study had a high prevalence (one-third) of patients with an ICD/CRT-D. At present, an ICD is the principle therapy in HF patients for preventing sudden cardiac death. It is increasingly used due to the extended indication for primary prevention. However, ICD-specific problems, such as frequent shocks and a poor understanding of ICD therapy, increase depressive symptoms and reduce the quality of life for the ICD patients [39,48–50]. Our main study showed that an ICD implantation was significantly associated with depression [26]. Furthermore, the prevalence of depression increased as the NYHA functional class grade increased [4]. In our study, 18 of 23 patients (78%) with NYHA class III/IV at discharge were diagnosed with depression by the Zung SDS. The presence of an ICD/CRT-D and NYHA functional class III/IV may have confounded the association between depression and the primary outcome. Therefore, depression alone was thought not to be a predictor in this study after adjusting for multiple variables.

State anxiety is a transient mental or emotional reaction to several stressors, including medical illness. In a sense, it is thought to be a normal reaction in hospitalized patients and an inevitable result of hospitalization. A Japanese report showed that anxiety has been reported to be independently associated with rehospitalization due to worsened HF in outpatients with stable HF [44]. However, in general, an association between anxiety and mortality or long-term cardiac events in patients with HF has not been found [16–19]. Katon et al. suggested that the combination of depression and anxiety is associated with poor treatment adherence and increased medical complications in patients with chronic medical illness, which may be a severe consequence [51]. Anxiety and depression are different disorders, and the way in which their mechanisms may interact in the development of cardiac events or death are not understood. In the real world, however, psychological factors may cluster together within individuals to increase the risk of subsequent medical events [21]. There is a possibility that patients with higher psychological distress are selected by combining anxiety with depression.

In our study, HF was a major cause of death, and the rate of HF was significantly higher in patients with both depression and anxiety than in those with either depression or anxiety only or those with no symptoms. Although its pathophysiologic mechanisms are not completely understood, psychological distress may affect the treatment adherence behavior in patients with HF [52]. Poor adherence to treatment is associated with increased morbidity and mortality in patients with HF [53]. Clustered depression and anxiety can be a stronger predictive marker of the severity of the illness or poor prognosis than depression alone in hospitalized patients with HF. This cluster may also be an important marker for psychological distress, particularly in hospitalized patients with HF.

Study limitations

There were some limitations in this study. First, this was a single-center cohort study. The clinical characteristics of our patients might not reflect those of general cardiovascular patients with HF. Second, the patients admitted to our hospital were not consecutively enrolled in our main study. Many patients who received emergent or intensive care were not enrolled because they could not complete the questionnaires. Third, the questionnaires were not completed prior to discharge. The primary aim of our main study was to evaluate the prevalence and distribution of depression in hospitalized patients. Moreover, the length of the hospital stay in our patients ranged from a few days to several months because the severity of HF or comorbidities was heterogeneous. For a long-term prognosis, the assessment just before discharge might be more appropriate. However, previous studies have demonstrated that depression at the time of hospitalization, not prior to discharge, is associated with a poorer prognosis in patients with cardiovascular disease [54–57]. Fourth, the number of subjects was relatively small. Therefore, subgroup analysis was not feasible.

Conclusions

Our results showed that clustered depression and anxiety were predictors of death from any cause or rehospitalization due to worsened HF and refractory arrhythmia in patients with HF. This cluster may be an important marker for poor outcomes in patients with HF.

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Conflict of interest

None declared.

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Original Article

Effect of intravenous amiodarone on QT and T peak–T end dispersions in patients with nonischemic heart failure treated with cardiac resynchronization-defibrillator therapy and electrical storm

Masataka Ogiso, MD[a], Atsushi Suzuki, MD[a], Tsuyoshi Shiga, MD[a,*], Kenji Nakai, MD[b], Morio Shoda, MD[a], Nobuhisa Hagiwara, MD[a]

[a] Department of Cardiology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
[b] Department of Internal Medicine of Dentistry, Iwate Medical University, Morioka, Japan

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ABSTRACT

Background: The effect of intravenous amiodarone on spatial and transmural dispersion of ventricular repolarization in patients receiving cardiac resynchronization therapy (CRT) remains unclear.
Methods: We studied 14 patients with nonischemic heart failure who received CRT with a defibrillator, experienced electrical storm and were treated with intravenous amiodarone. Each patient underwent 12-lead electrocardiography (ECG) and 187-channel repolarization interval-difference mapping electrocardiography (187-ch RIDM-ECG) before and during the intravenous administration of amiodarone infusion.
Results: A recurrence of ventricular tachyarrhythmia was observed in 2 patients during the early period of intravenous amiodarone therapy. Intravenous amiodarone increased the corrected QT interval (from 470 ± 52 ms to 508 ± 55 ms, $P=0.003$), but it significantly decreased the QT dispersion (from 107 ± 35 ms to 49 ± 27 ms, $P=0.001$), T peak–T end (Tp–e) dispersion (from 86 ± 17 ms to 28 ± 28 ms, $P=0.001$), and maximum inter-lead difference between corrected Tp–e intervals as measured by using the 187-ch RIDM-ECG (from 83 ± 13 ms to 50 ± 19 ms, $P=0.001$).
Conclusions: Intravenous amiodarone suppressed the electrical storm and decreased the QT and Tp–e dispersions in patients treated by using CRT with a defibrillator.

1. Introduction

Cardiac resynchronization therapy (CRT) reduces mortality and morbidity in selected heart failure patients with impaired left ventricular (LV) function and cardiac dyssynchrony [1]. Most patients receive CRT with a defibrillator (CRT-D) because the indications for an implantable cardioverter-defibrillator (ICD) overlap with those for CRT. Electrical storm, which is commonly defined as the occurrence of 3 or more separate episodes of ventricular tachyarrhythmia requiring ICD therapies within 24 h [2], is associated with worse heart failure-related morbidity and survival among patients who receive CRT-D [3,4].

CRT may increase LV transmural dispersion of repolarization, leading to ventricular tachyarrhythmia and electrical storm induced by epicardial LV pacing [4–6]. Moreover, some reports have demonstrated that ICD shocks alone can cause an increase in QT dispersion, which may contribute to the proarrhythmic effects of ICD shocks such as electrical storm [7,8]. Myocardial ischemia increases the dispersion of repolarization and may result in shock-induced arrhythmia [9,10].

Intravenous amiodarone is widely used in the treatment of electrical storm [2]. However, few clinical studies have evaluated the effect of intravenous amiodarone on the spatial and transmural dispersion of ventricular repolarization in patients treated with CRT.

The aim of this study was to evaluate the effect of intravenous amiodarone on the electrocardiographic parameters of dispersion of ventricular repolarization in patients with nonischemic heart failure treated with CRT-D and electrical storm.

2. Methods

We studied 14 patients treated with CRT-D who were admitted to our hospital because of electrical storm (Table 1). Patients who were in atrial fibrillation were excluded. Amiodarone diluted with

* Corresponding author. Tel.: +81 3 3353 8111; fax: +81 3 3356 0441.
E-mail address: mshiga@hij.twmu.ac.jp (T. Shiga).

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Table 1
Baseline characteristics in 14 nonischemic heart failure patients and electrical storm treated with CRT-D.

Men (n)	11
Age (years)	67 ± 12
Indication for ICD	
Secondary prevention	10
Primary prevention	4
Underlying heart disease	
Idiopathic dilated cardiomyopathy	8
End-stage hypertrophic cardiomyopathy	3
Other	3
NYHA functional class on admission	
II/III/IV	8/4/2
LVEF (%)	27 ± 3
Plasma BNP (pg/mL)	617 ± 547
eGFR (mL/min/1.73 m^2)	52.5 ± 39.0
Medications on admission	
Beta-blockers	12
ACE inhibitors/ARBs	12
Spironolactone	8
Loop diuretics	11
Amiodarone	8

Values are represented as n or mean ± SD.
ICD, implantable cardioverter-defibrillator; CRT-D, cardiac resynchronization therapy with ICD; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; and ARB, angiotensin II receptor blocker.

5% glucose was administered as a loading dose of 2.0 mg/kg for 10 min and was subsequently infused continuously as a maintenance dose of 0.5 mg/kg/h. Twelve-lead electrocardiography (ECG) was performed by using a standard digital recorder (CardiofaxV, Nihon Kohden Co., Tokyo, Japan) at a gain of 20 mm/mV and a speed of 50 mm/s; a 187-channel repolarization interval-difference mapping electrocardiograph (187-ch RIDM-ECG, Fukuda Denshi Co. Ltd., Tokyo, Japan) was also used. The data from both procedures were recorded before and during the intravenous infusion of amiodarone. Additionally, blood samples were drawn to assess the concentration of amiodarone in the patients' plasma. This study was approved by the institutional review board of the Tokyo Women's Medical University (approval no. 2036), and all patients provided written informed consent.

The QT intervals and T-peak to T-end (Tp–e) intervals were measured by using leads II and V2 of the 12-lead ECG. The QT interval was obtained from the onset of the QRS complex to the end of the T wave. The corrected QT interval (QTc) was calculated using the Bazett formula. QT dispersion was defined as the difference between the maximum and minimum QT intervals of the 12 ECG leads. The Tp–e interval was obtained from the peak of the T wave to the end of the T wave, which corresponded to the bottom of the T wave in cases of negative or biphasic T waves. The Tp–e dispersion was obtained by assessing the difference between the maximum and minimum Tp–e intervals of the 12 ECG leads (Fig. 1). Measurements of the recovery time (RT) and Tp–e intervals according to the results of the 187-ch RIDM-ECG were previously described in detail [7], and the corrected RT and corrected Tp–e intervals were calculated by using the Bazett formula. The maximum inter-lead differences between corrected RT intervals and between corrected Tp–e intervals were automatically calculated based on the difference between the maximum and minimum values in this system. The corrected RT and Tp–e interval difference maps were displayed as a color-coordinated map according to time differences.

The data are presented as the mean ± SD. The parameters were compared before and during the intravenous amiodarone infusion by using the Mann–Whitney U test, and a P-value < 0.05 was considered significant.

3. Results

Among the 14 patients who received intravenous amiodarone for the treatment of electrical storm, 1 patient received an inotropic agent (intravenous dopamine) and 2 patients received a sedative agent concomitant with the administration of intravenous amiodarone. The other patients continued to receive the same dose of beta-blockers and other cardiovascular drugs during the intravenous amiodarone treatment as they did prior to treatment. Ventricular tachyarrhythmia that required ICD shock recurred in 2 patients after the initiation of amiodarone infusion but it was not observed after the initial 16 h of continuous infusion. No recurrence of ventricular tachyarrhythmia that required ICD therapy occurred in the other patients during the intravenous amiodarone infusion. The mean treatment period of intravenous amiodarone was 105 ± 98 h. The results of the 12-lead ECG and the 187-ch RIDM-ECG recorded during the intravenous amiodarone infusion were obtained 26 ± 19 h after the start of therapy.

The 12-lead ECG and 2-dimensional geometrical maps for corrected RT interval difference and corrected Tp–e interval difference obtained by using 187-ch RIDM-ECG before and during the intravenous amiodarone infusion for representative cases are shown in Figs. 1 and 2 respectively. The mean value of QTc measured by using the 12-lead ECG increased during the intravenous administration of amiodarone. By contrast, the maximum value of the QT interval among the 12 leads decreased, and its minimum value increased during the intravenous administration of amiodarone. Although the mean value of the Tp–e interval measured by using the 12-lead ECG was not affected during the intravenous administration of amiodarone, the maximum value of the Tp–e interval among the 12 leads decreased, and its minimum value increased during the intravenous administration of amiodarone. Additionally, QT dispersion and Tp–e dispersion significantly decreased during the intravenous amiodarone administration. The maximum inter-lead difference between the corrected Tp–e intervals, but not the corrected RT intervals, as measured by using 187-ch RIDM-ECG, significantly decreased during the intravenous infusion of amiodarone (Table 2).

These effects of intravenous amiodarone on ECG parameters were similar between the patients who received and those who did not receive prior oral amiodarone treatment (Table 2).

4. Discussion

This study showed that intravenous amiodarone mostly suppressed ventricular tachyarrhythmia and increased the QTc, but not the Tp–e interval. Moreover, intravenous amiodarone decreased QT dispersion, Tp–e dispersion, and the maximum inter-lead difference between the corrected Tp–e intervals, as measured by using the 187-ch RIDM-ECG, in patients with CRT-D and electrical storm. Among our patients, prior oral amiodarone therapy did not affect the change in QT dispersion, Tp–e dispersion, or maximum inter-lead difference between the corrected Tp–e intervals before or during the intravenous amiodarone treatment.

Amiodarone is capable of modifying the activation pattern of the ventricle during biventricular pacing in patients receiving CRT because it affects both ventricular depolarization and repolarization. This may be reflected in the repolarization parameters of ECG, such as the QT interval. Interestingly, intravenous amiodarone treatment decreased the maximum QT and Tp–e intervals and increased the minimum QT and Tp–e intervals. These effects of amiodarone on ECG parameters might not be due to an equal

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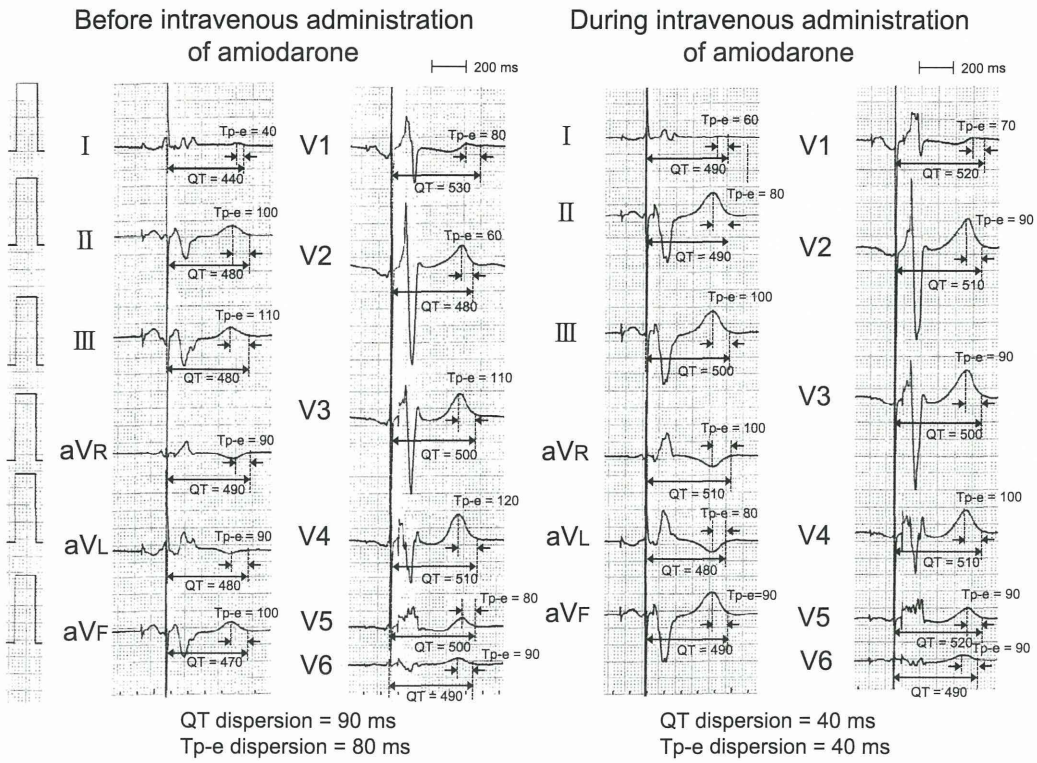

Fig. 1. ECG readings. Representative 12-lead ECG (50 mm/s) images before and during intravenous administration of amiodarone infusion in a patient with CRT-D and electrical storm. The results of the patient were set to an AV delay of 150 ms and a VV delay of 45 ms. QT dispersion = maximum QT interval − minimum QT interval among 12 leads. Tp–e dispersion = maximum Tp–e interval − minimum Tp–e interval among 12 leads.

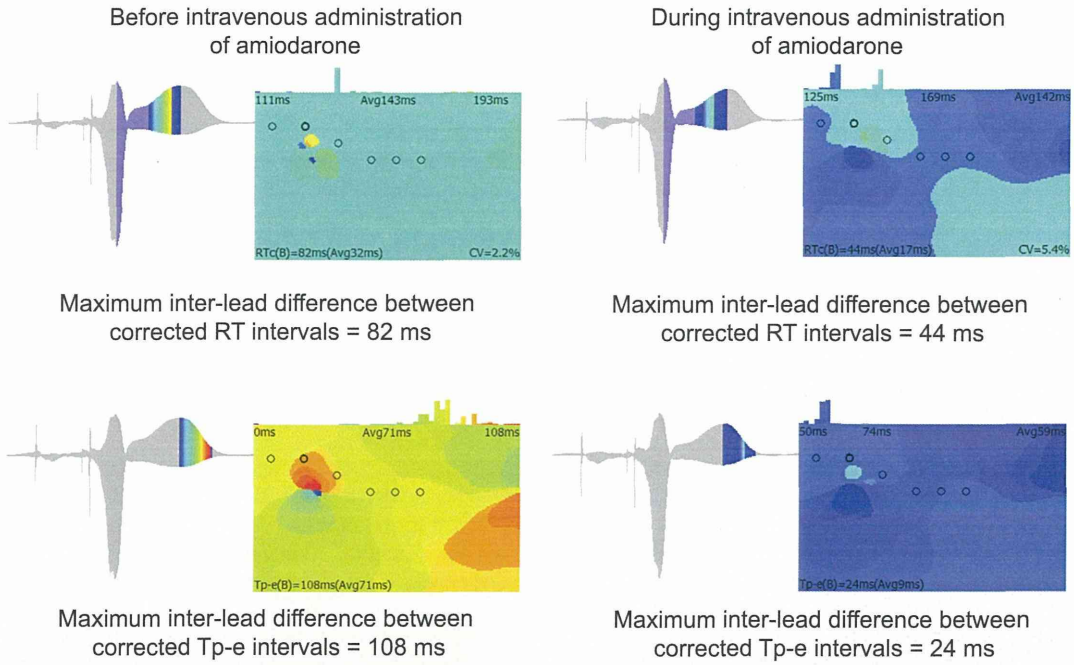

Fig. 2. Interval difference maps. Representative corrected RT interval difference map and corrected Tp–e interval difference map before and during intravenous administration of amiodarone infusion in a patient with CRT-D and electrical storm. The results of the patient were set to an AV delay of 140 ms and a VV delay of 20 ms. The differences from the smallest corrected RT interval or corrected Tp–e interval were scaled according to color, with blue indicating < 40 ms, yellow indicating 40–60 ms, and red indicating > 60 ms. Maximum inter-lead difference between corrected RT intervals = maximum corrected RT interval − minimum RT interval. Maximum inter-lead difference between corrected Tp–e intervals = maximum Tp–e interval − minimum Tp–e interval (measured on the 187-ch RIDM-ECG image).

decrease in transmural dispersion of repolarization at any region in the ventricle; instead, they might be the results of counterbalancing the heterogeneity of ventricular repolarization. A significant decrease in QT dispersion, Tp–e dispersion, and maximum inter-lead difference between corrected Tp–e intervals (by using 187-ch RIDM-ECG) supports the hypothesis that intravenous amiodarone decreases the spatial dispersion of ventricular repolarization.

The mean value of the inter-lead difference between corrected RT intervals determined by using 187-ch RIDM-ECG decreased

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Table 2
Electrocardiographic parameters before and during intravenous amiodarone infusion in 14 nonischemic heart failure patients and electrical storm treated with CRT-D.

	Before amiodarone	During amiodarone	*P* value
12-Lead ECG			
RR (ms)	870 ± 101	851 ± 89	0.593
QRS duration (ms)	149 ± 20	165 ± 21	0.003
QTc (ms)	470 ± 52	508 ± 55	0.003
Maximum QT (ms)	510 ± 49	478 ± 37	0.006
Minimum QT (ms)	403 ± 34	429 ± 39	0.006
QT dispersion (ms)	107 ± 35	49 ± 27	0.001
Tp–e (ms)	101 ± 18	107 ± 18	0.217
Max Tp–e (ms)	145 ± 27	121 ± 28	0.027
Minimum Tp–e (ms)	59 ± 18	92 ± 12	0.001
Tp–e dispersion (ms)	86 ± 17	28 ± 28	0.001
Prior oral amiodarone (+), n=8			
RR (ms)	846 ± 102	811 ± 53	0.362
QRS duration (ms)	148 ± 23	168 ± 22	0.017
QTc (ms)	469 ± 58	522 ± 64	0.025
Maximum QT (ms)	506 ± 51	478 ± 43	0.049
Minimum QT (ms)	396 ± 41	426 ± 45	0.030
QT dispersion (ms)	111 ± 36	51 ± 24	0.012
Tp–e (ms)	103 ± 17	114 ± 19	0.125
Max Tp–e (ms)	148 ± 26	131 ± 32	0.235
Minimum Tp–e (ms)	65 ± 19	98 ± 12	0.012
Tp–e dispersion (ms)	84 ± 13	34 ± 35	0.017
Prior oral amiodarone (−), n=6			
RR (ms)	903 ± 90	905 ± 99	0.785
QRS duration (ms)	152 ± 16	161 ± 20	0.066
QTc (ms)	472 ± 43	491 ± 33	0.043
Maximum QT (ms)	515 ± 47	480 ± 28	0.043
Minimum QT (ms)	412 ± 19	433 ± 29	0.068
QT dispersion (ms)	103 ± 32	46 ± 30	0.043
Tp–e (ms)	100 ± 18	98 ± 12	0.891
Maximum Tp–e (ms)	142 ± 28	106 ± 10	0.042
Minimum Tp–e (ms)	53 ± 13	85 ± 8	0.042
Tp–e dispersion (ms)	89 ± 20	21 ± 13	0.027
187-ch RIDM-ECG			
Inter-lead difference between corrected RT (ms)	83 ± 19	68 ± 26	0.064
Inter-lead difference between corrected Tp–e (ms)	83 ± 13	50 ± 19	0.001
Prior oral amiodarone (+), n=8			
Inter-lead difference between corrected RT (ms)	87 ± 19	69 ± 28	0.176
Inter-lead difference between corrected Tp–e (ms)	86 ± 14	47 ± 24	0.012
Prior oral amiodarone (−), n=6			
Inter-lead difference between corrected RT (ms)	78 ± 18	68 ± 22	0.248
Inter-lead difference between corrected Tp–e (ms)	80 ± 9	54 ± 7	0.028
Plasma drug concentration			
Prior oral amiodarone (+), n=8			
Amiodarone (μg/mL)	0.36 ± 0.36	1.67 ± 0.79	
Desethylamiodarone (μg/mL)	0.36 ± 0.33	0.74 ± 0.27	
Prior oral amiodarone (−), n=6			
Amiodarone (μg/mL)	–	1.45 ± 0.69	
Desethylamiodarone (μg/mL)	–	0.51 ± 0.32	

Values are represented as mean ± SD.
ECG, electrocardiography; QTc, corrected QT interval; RT, recovery time; Tp–e; T peak–T end; and 187-ch RIDM-ECG, 187-channel repolarization interval-difference mapping electrocardiograph.

during the intravenous administration of amiodarone, but this difference was not statistically significant. In contrast, QT dispersion on the 12-lead ECG significantly decreased. The RT interval was defined as the time difference between the R-wave peak and the T-wave peak of the relative electrical current density of the variable-moment dipole current, which was calculated from the 187-channel electrical potentials on the basis of the Coulomb Law [11,12]. Therefore, the R-wave and T-wave peaks on the 187-ch RIDM-ECG images were not identical to those on the 12-lead ECG image. The inter-lead difference between the corrected RT intervals obtained from the 187-ch RIDM-ECG image may be less likely to be modified by the effect of amiodarone on depolarization and repolarization of the ventricle.

The acute effects of amiodarone are the blockade of the L-type calcium inward current; the sodium inward current (I_{Na}), with a high affinity for its inactivated state; and the rapid and slow components of the delayed rectifier potassium current (I_{Kr} and I_{Ks}). In contrast, its chronic effect is mediated by prolonging the action potential duration (APD) through a decrease in the potassium channel density, especially I_{Ks} and transient outward current [13]. A single intravenous bolus of amiodarone does not prolong the QRS duration or QTc in humans, as observed on ECG [14,15]. In an experimental study, amiodarone produced little change in the APD of epicardial and endocardial tissues, but it shortened the APD of the M-region tissue via the blockade of late I_{Na}, leading to a decrease in the transmural dispersion of repolarization in the

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canine ventricle [16]. The results of another experimental study revealed that amiodarone suppressed inducible arrhythmia, with a decrease in the Tp–e and the transmural dispersion of APD secondary to the inhibition of both the I_{Kr} and the late I_{Na} at high concentrations of the drug (1–10 μM) in rabbit heart in which the late I_{Na} was augmented in the presence of sea anemone toxin [17]. Although the mechanisms are not well understood, the acute effect of amiodarone in inhibiting the late I_{Na} and counterbalancing APD prolongation through the inhibition of I_{Kr} may play a role in the beneficial effect of repolarization on LV spatial and transmural dispersion in patients with heart failure.

A recurrence of ventricular arrhythmia requiring ICD therapy was observed in 2 patients during the early period of intravenous amiodarone therapy. This recurrence may be due to the slow uptake of amiodarone into heart tissue because of its pharmacokinetic characteristics, which also accounts for its delayed antiarrhythmic effects [14]. In this study, we observed the pharmacological effect of amiodarone on the parameters of dispersion of ventricular repolarization, but it was unclear whether these effects were closely related to the therapeutic value of amiodarone for suppression of ventricular arrhythmias, such as electrical storm. To clarify this issue, further clinical investigation is necessary.

In conclusion, intravenous amiodarone suppressed electrical storm and decreased QT and Tp–e dispersions in patients with nonischemic heart failure treated with CRT-D and electrical storm. These effects may partially result from a decrease in spatial dispersion of ventricular repolarization.

Conflict of interest

The authors have no conflicts of interest to declare.

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Chronic kidney disease and long-term outcomes of myocardial infarction ☆

Michitaka Nagashima [1], Nobuhisa Hagiwara [1], Ryo Koyanagi [1], Jun-ichi Yamaguchi [1], Atsushi Takagi [1], Erisa Kawada-Watanabe [1], Tsuyoshi Shiga [1], Hiroshi Ogawa *,[1]

Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, Tokyo, Japan

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ABSTRACT

Background: Although chronic kidney disease (CKD) is a risk factor for cardiovascular disease, information about myocardial infarction (MI) with CKD is limited in the acute revascularization era.
Methods: To clarify the relationship between CKD and long-term outcomes of MI, consecutive 4550 patients with acute MI treated at 17 participating hospitals were analyzed. The primary study outcome was death from any cause, and a secondary endpoint was the first appearance major adverse cardiovascular events.
Results: Acute revascularization therapies were performed in 75.2% of the patients and the mean left ventricular ejection fraction (LVEF) was 53%. The median follow-up was 4.1 years (follow-up rate, 95.2%). Patients were divided into four categories (<45.0, 45.0 to 59.9, 60.0 to74.9, and ≥75.0 mL/min per 1.73 m^2 of body-surface area) according to the glomerular filtration rate (GFR) estimated by the Modification of Diet in Renal Disease equation. A total of 1941 (42.7%) patients had an estimated GFR of <60.0 mL/min per 1.73 m^2. Mortality rates increased with declining estimated GFR. Unadjusted hazard ratios for total and cardiovascular death in the group with an estimated GFR of 45.0 to 59.9 mL/min per 1.73 m^2 using the group with an estimated GFR of ≥75.0 mL/min per 1.73 m^2 as the reference were 1.63 (95% CI, 1.28 to 2.07) and 2.09 (95% CI, 1.45 to 3.01), respectively.
Conclusions: Even early-stage CKD should be considered a powerful risk factor for long-term cardiovascular death after acute MI with preserved LVEF in the acute revascularization era.

1. Introduction

Renal impairment is a worldwide public health issue, with increasing incidence, expense and adverse outcomes [1]. The National Kidney Foundation defines chronic kidney disease as kidney damage or a glomerular filtration rate (GFR) of <60.0 mL/min per 1.73 m^2 of body-surface area for over three months, irrespective of cause [2]. This definition highlights the fact that strategies to improve outcomes require a global effort directed towards the earlier stages of chronic kidney disease (CKD). Coexisting CKD in patients with established cardiovascular disease is also associated with long-term adverse outcomes [3–6]. Patients on dialysis who have acute myocardial infarction (AMI) have high mortality from cardiac cause and poor long-term survival [7]. However, information is scarce about long-term risks associated with CKD which does not require dialysis in patients with AMI. This is because the methods of previous cardiovascular studies such as design, setting and participants are limited.

The Heart Institute of Japan, Department of Cardiology (HIJC) project is a collaborative effort towards developing a domestic epidemiologic database and improving the quality of care for patients with cardiovascular disease [6,8–10]. As part of that project, we evaluated the prevalence of CKD using the value of estimated GFR from survivors of AMI who had not received dialysis to clarify the relationship between early-stage chronic kidney disease and long-term outcomes of AMI.

2. Materials and methods

The HIJC investigators registered and prospectively followed up 8335 patients with coronary artery disease treated after admission to 17 hospitals, including Department of Cardiology, the Heart Institute of Japan, Tokyo Women's Medical University between 1999 and 2004. Among them, the cohort used in the present study involved 4550 patients with AMI, who were discharged alive and who had not received maintenance dialysis at entry. AMI was diagnosed based on the presence of symptoms, high cardiac enzyme levels, and electrocardiographic changes according to then-current criteria [11]. The study proceeded according to the principles of the Declaration of Helsinki, and the protocol was approved by the institutional review board or ethics committee at each participating center. All participating patients provided written or oral informed consent before study enrollment. Because the HIJC project is mainly for observational purposes, treatment strategies were left to the discretion of the attending physicians.

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* Corresponding author at: Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. Tel.: +81 3 3353 8111; fax: +81 3 3356 0441.
E-mail address: mogawa@hij.twmu.ac.jp (H. Ogawa).
[1] For the Heart Institute of Japan, Department of Cardiology (HIJC) Investigators.

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