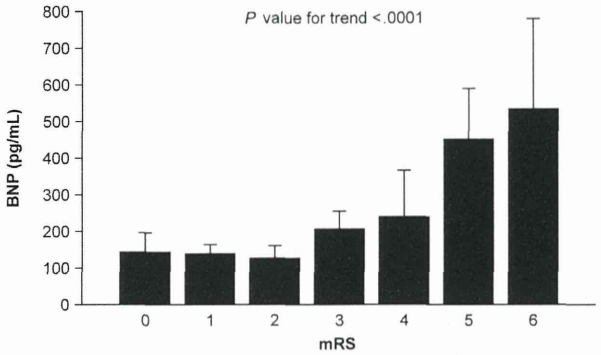

Figure 3. *Correlation between BNP levels and mRS scores. BNP levels increased as the mRS score increased. Abbreviations: BNP, brain natriuretic peptide; mRS, modified Rankin Scale.*

that BNP may be related to hyponatremia-associated natriuresis following these events. Increased noradrenaline may also promote the secretion of BNP in these patients; similar mechanisms may affect BNP levels in AIS patients with large infarcts because large cerebral infarction can increase noradrenaline release in the case of subarachnoid hemorrhage.

We demonstrated that BNP levels were positively correlated with mRS scores. In a recent report, plasma BNP levels were strongly associated with cardiogenic embolic stroke and functional outcomes at 6 months after ischemic stroke.[22] Our results were consistent with the results in this report. DWI lesion size and admission NIHSS scores have also been associated with BNP levels.[23-25] In our study, infarct size was associated with BNP levels, whereas NIHSS scores were not. These results suggest that stroke subtype (CE) and infarct size may affect BNP levels more than NIHSS scores. In patients with AIS, elevated serum BNP levels, on admission, may not only confirm a CE etiology of stroke event but may also signal an increased risk for poor long-term outcomes.[6,8,26]

BNP levels have not been previously reported to be associated with $CHADS_2$ scores. In previous studies, each component of the $CHADS_2$ score was established as a predictive factor of poor short- or long-term functional outcomes in stroke patients.[27-29] High CHADS2 scores, associated with increased BNP levels, may reflect

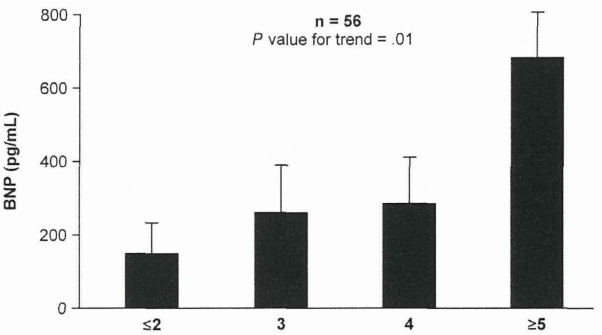

Figure 4. *Correlation between BNP levels and $CHADS_2$ scores. As $CHADS_2$ score increased, the BNP level also increased. Abbreviation: BNP, brain natriuretic peptide.*

advanced cardiac dysfunction. Thus, serum BNP levels may be considered to be surrogate markers of CE, infarct size, and poor outcomes in AIS patients and of stroke risk in AF patients.

In summary, serum BNP levels are associated with CAD, AF, renal function, and outcomes in AIS patients and are strongly associated with CE. There was a significant correlation between BNP levels and infarct size and were correlated with $CHADS_2$ scores in AF patients. Thus, BNP might be a useful marker or predictor for the diagnosis of CE, outcome, and infarct size in AIS patients and stroke risk in AF patients.

Acknowledgment: We thank Mr Katsunori Shimada, PhD (STAZ Institute, Inc., Tokyo), for assisting with the statistical analysis.

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Journal of Arrhythmia 31 (2015) 1–5

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

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

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ARTICLE INFO

Article history:
Received 4 May 2013
Received in revised form
13 January 2014
Accepted 29 January 2014
Available online 3 April 2014

Keywords:
Amiodarone
Cardiac resynchronization therapy
Dispersion
QT interval
T peak–T end

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

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http://dx.doi.org/10.1016/j.joa.2014.01.006
1880-4276/

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

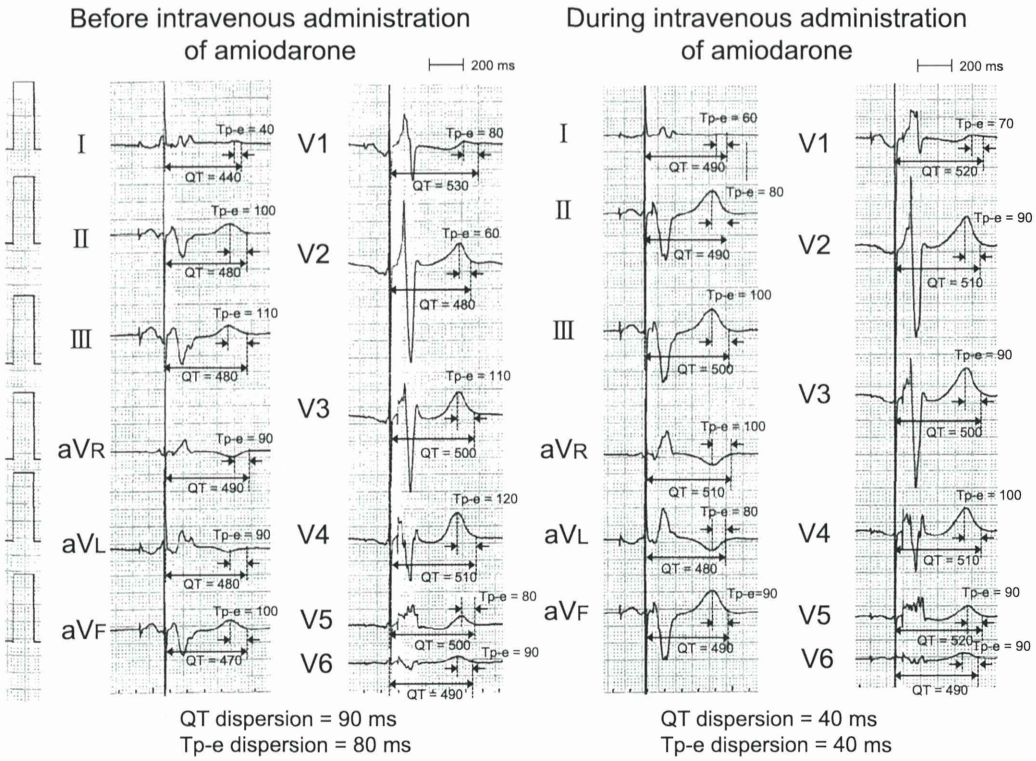

Fig. 1. ECG readings. Representative 12-lead ECG (50 mm/s) images before and during intravenous administration of amiodarone infusion in a patient with CRT-D and electrical storm. The results of the patient were set to an AV delay of 150 ms and a VV delay of 45 ms. QT dispersion = maximum QT interval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

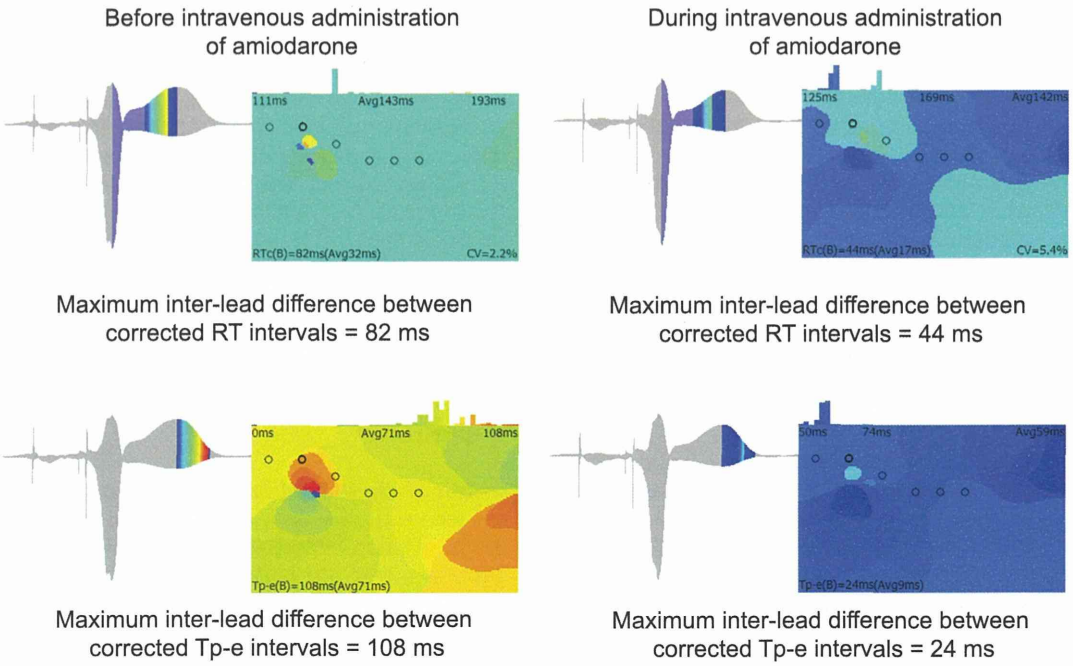

Fig. 2. Interval difference maps. Representative corrected RT interval difference map and corrected Tp–e interval difference map before and during intravenous administration of amiodarone infusion in a patient with CRT-D and electrical storm. The results of the patient were set to an AV delay of 140 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 counter-balancing 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

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

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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Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Imaging

The Speckle Tracking Imaging for the Assessment of Cardiac Resynchronization Therapy (START) Study

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Background: We sought to identify the feasibility of speckle tracking echocardiography (STE) to predict cardiac resynchronization therapy (CRT) responders in a prospective multicenter study.

Methods and Results: Patients who were newly implanted with a CRT device were enrolled. Time (T) from QRS to maximum peak radial and circumferential strain (CS) in 6 segments on the left ventricular (LV) short-axis plane, and to the maximum peak of longitudinal strain in 18 segments on 3 apical LV planes was measured (T_{max}). In segments with multiple peaks on the time-strain curves, time to the first peak (T_{first}) was also assessed. Difference in T between the earliest and latest segment and standard deviation (SD) of T in each strain component were assessed. CRT responders were defined as having LV end-systolic volume reduction >15% at 6 months after CRT. Clinical outcomes were assessed with a composite endpoint of death from cardiac causes or unplanned hospitalization for heart failure. Among 180 patients, 109 patients were identified as responders. T_{first}-SD of CS >116 ms was selected as the best independent predictor of CRT responders (P<0.001, hazard ratio=9.83, 95% confidence interval 3.78–25.6). In addition, T_{first}-SD of CS was associated with the clinical endpoints.

Conclusions: This prospective multicenter study revealed the high feasibility of dyssynchrony assessment by STE, which may improve the ability to predict CRT responders. (*Circ J* 2015; **79:** 613–622)

Key Words: Cardiac resynchronization therapy; Heart failure; Speckle tracking echocardiography

Cardiac resynchronization therapy (CRT) is an important treatment option for patients with drug refractory heart failure, but several large trials have indicated a low clinical response (≈70% of patients).[1–3] The primary concept of CRT is improvement of intraventricular dyssynchrony of the left ventricle, and echocardiography seems to be an ideal modality for predicting responders to CRT. However, echocardiographic dyssynchrony parameters determined by M-mode, Doppler, and tissue Doppler imaging (TDI) in prospective multicenter studies have shown disappointing results,[4–7] following which,

Received July 31, 2014; revised manuscript received October 29, 2014; accepted November 20, 2014; released online December 27, 2014
Time for primary review: 40 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0842

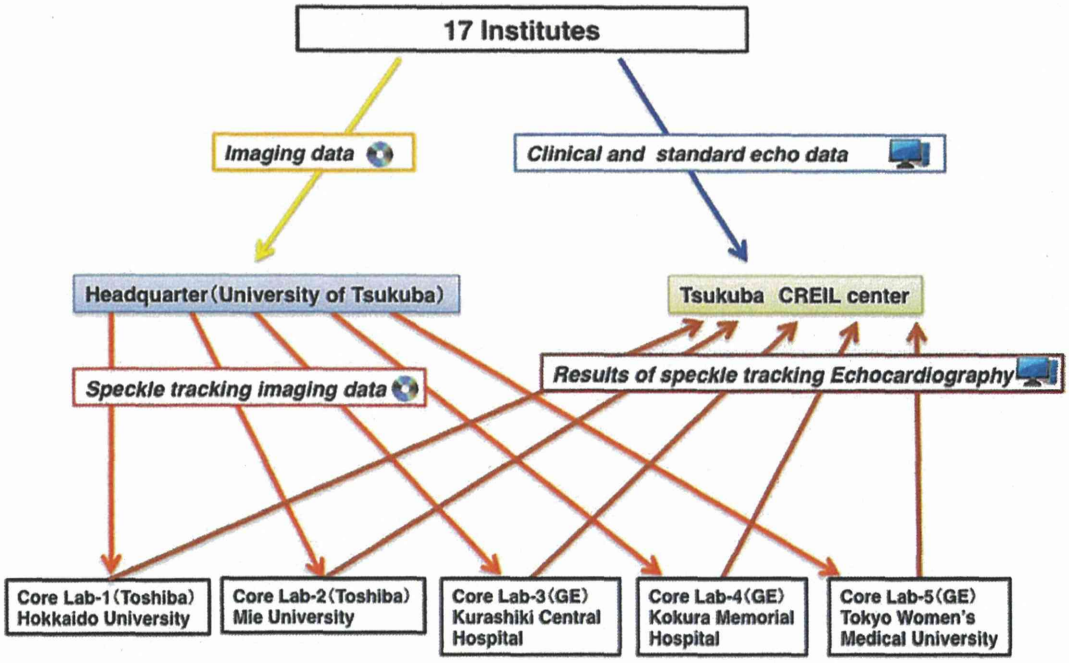

Figure 1. Data flow and management in the Speckle Tracking Imaging for the Assessment of Cardiac Resynchronization Therapy (START) study (for details, see text).

assessments of mechanical dyssynchrony by echocardiography have not been included in the guidelines for CRT.

Speckle tracking echocardiography (STE) has the potential to accurately predict responders to CRT, and some studies have suggested that STE parameters improve prediction of CRT responders.[8–11] However, well-performed, prospective, multicenter studies have shown no evidence of improved prediction. Moreover, the directions of strain parameters measured in these studies were variable (longitudinal, circumferential, radial, or transverse), and uncertainty remains as to the best approach to determine dyssynchrony.

The regional time-strain curve is sometimes complex, with multiple peaks, and identification of which peak to choose can be confusing. Further, there is no agreement on which peak is correct, although many researchers have chosen the maximum peak.[12]

In addition, the very limited interinstitutional reproducibility of dyssynchrony parameters is an important and problematic issue.[6] Some investigators have shown time-to-peak analysis by tissue Doppler imaging to be nonreproducible.[13] Most multicenter studies of dyssynchrony assessments by STE used a core laboratory and showed acceptable reproducibility of STE analysis in that laboratory. However, reproducibility should be compared among several laboratories to provide objective data. Accordingly, we conducted a prospective multicenter study to assess the feasibility of STE for the prediction of CRT responders while maintaining an objective manner of analysis.

Methods

Study Design

The Speckle Tracking Imaging for the Assessment of Cardiac Resynchronization Therapy (START) study was a multicenter prospective cohort study of patients undergoing CRT in Japan. Patients were enrolled from 17 Japanese centers between September 2009 and August 2011, and clinical follow-up was completed in September 2012. The study was approved by the local ethics committee of each participating institution. All patients provided written informed consent.

Study Population

Patients were enrolled based on criteria that included congestive heart failure refractory to optimal medical therapy and QRS duration ≥120 ms, NYHA class II, III or IV and left ventricular (LV) ejection fraction ≤35%. Patients were excluded at the baseline evaluation if they were expected to die within 1 year because of noncardiac disease, if they were scheduled for catheter intervention or cardiac surgery including cardiotomy or coronary bypass, or if they were expected to be lost to follow-up during the first year after CRT. We also excluded patients in chronic atrial fibrillation with irregular rhythm, except for those with regular rhythm because of ventricular pacing or escape rhythm with complete atrioventricular conduction block. Patients were scheduled to undergo echocardiographic studies with NYHA functional class assessment before and at 1 week and 6 months after CRT. Patients were followed up for at least 12 months.

CRT Responses and Clinical Outcomes

Two responses, LV reverse remodeling and clinical outcomes, were assessed. First, a volume responder to CRT was defined as a patient with reverse remodeling as indicated by ≥15% reduction of LV end-systolic volume at 6 months after CRT. Second, clinical outcomes were assessed with the endpoints of composite of death from cardiac causes or unplanned hospitalization for heart failure.

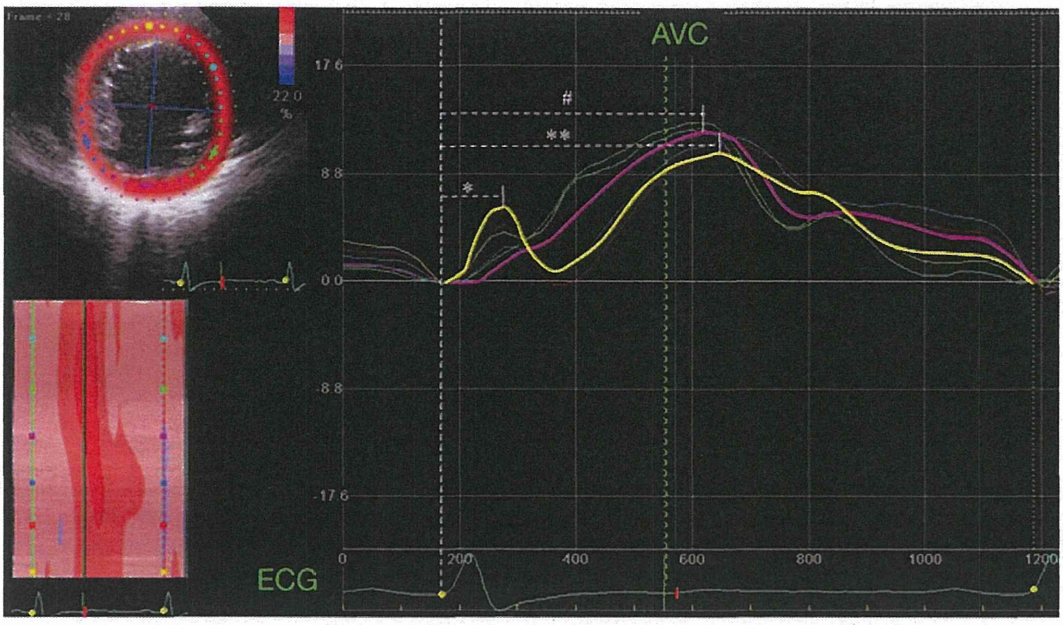

Figure 2. Regional contraction delay on time-strain curves on the midventricular short-axis view obtained from a patient with idiopathic dilated cardiomyopathy and left bundle branch block. The yellow curve, which was obtained from the anteroseptal wall, shows a representative pattern with multiple strain peaks. Time from QRS onset to maximum strain (T_{max}) corresponds to the duration marked by ** and time from QRS onset to first peak (T_{first}) corresponds to the duration marked by *. The purple curve, which was obtained from the posterior wall, shows a representative pattern with a single strain peak, in which both T_{max} and T_{first} correspond to the duration marked by #. The green dashed line indicates the timing of end-systole. AVC, aortic valve closure; ECG, electrocardiogram.

Data Flow

Data flow is summarized in **Figure 1**. The Tsukuba Critical Path Research and Education Integrated Leading (CREIL) Center at the University of Tsukuba (http://md.tsukuba.ac.jp) performed data management. Clinical and standard echocardiographic data were obtained according to the study protocol and registered to the database in the CREIL center via the internet from each institution. In this study, echocardiographic systems were limited to 2 vendors: GE Healthcare (Horton, Norway) and Toshiba Medical Systems (Tochigi, Japan). The 5 core laboratories were assigned to analyze STE data only without any knowledge of the clinical data; 3 core laboratories (Tokyo Women's University, Kokura Memorial Hospital, and Kurashiki Central Hospital) were assigned to analyze data from the GE systems, and the remaining 2 core laboratories (Hokkaido University and Mie University) analyzed the data from the Toshiba systems. STE data flow was as follows: a DVD with STE data sets was sent to the core laboratory specified for each institution by the study headquarters located at the University of Tsukuba. The results of STE analyses were registered to the database in the CREIL center via the internet from each core laboratory.

Conventional and Doppler Echocardiographic Studies

LV volumes (biplane modified Simpson's method), dimensions, and wall thickness; Doppler-derived parameters of LV diastolic function; mitral regurgitation severity, defined as the ratio of color Doppler mitral regurgitant jet area to left atrial area (mitral regurgitation index); and pressure gradient derived from tricuspid regurgitant flow were assessed by standard methods. In this study, 4 previously reported dyssynchrony parameters were assessed for their ability to identify CRT responders:[14] septal-to-posterior wall motion delay on the M-mode image (SPWMD), standard deviation of time from QRS to peak systolic velocity by tissue Doppler imaging in the ejection phase for 12 LV segments (Ts-SD), delay between time to peak systolic velocity by tissue Doppler imaging in ejection phase at the basal septal and lateral segments (Ts-LS), and interventricular mechanical delay (IMD), defined as the difference between LV pre-ejection period and RV pre-ejection period.

STE Studies

Images for STE studies were obtained in a LV short-axis plane at the papillary muscle level and in the apical 4-chamber, 2-chamber, and long-axis planes. The images were recorded at a minimum of 50 frames per second and were analyzed using workstations with vendor software packages (EchoPac PC v.7.0.1, GE Healthcare; 2D Wall Motion Tracking, Toshiba Medical Systems Co). Tanaka et al have showed that strain dyssynchrony analyses using different software (GE and Toshiba) were similarly able to predict responder to CRT.[15] On an end-systolic frame, a region of interest (ROI) was traced on the endocardial cavity interface by a point-and-click approach. The ROI was automatically selected to approximate the myocardium between the endocardium and epicardium. Further adjustment of the ROI was performed to ensure that all regions of the myocardium were included. Next, the software captured the myocardium and automatically tracked its motion and thickening on the subsequent frames. Finally, the myocardium was divided into 6 segments in each plane. Time-radial strain (RS) and time-circumferential strain (CS) curves were obtained from the 6 segments of the LV short-axis plane. Time-longitudinal