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ORIGINAL ARTICLE
Heart Failure

Significant Increase in the Incidence of Ventricular Arrhythmic Events After an Intrathoracic Impedance Change Measured With a Cardiac Resynchronization Therapy Defibrillator

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Background: Cardiac resynchronization therapy defibrillator (CRT-D) devices are now capable of monitoring changes in intrathoracic impedance. Intrathoracic impedance monitoring resulting in a fluid index threshold crossing has been proven to predict heart failure (HF) exacerbations. We retrospectively investigated the relationship between changes in intrathoracic impedance and the occurrence of arrhythmic events.

Methods and Results: From 282 patients with New York Heart Association class III or IV HF who were implanted with a CRT-D device with a fluid index feature based on intrathoracic impedance monitoring capabilities, arrhythmic events were retrospectively analyzed in terms of the threshold crossings. The patients were divided into 2 groups: those with fluid index threshold crossings and those without threshold crossings. A total of 4,725 tachyarrhythmic events were reported in 129 patients (46%), and there were 221 fluid index crossing events in 145 patients (51%) during 10.0±3.2 months. Tachyarrhythmic events were more frequently recorded in patients with threshold crossing events than in those who did not experience a threshold crossing (3,241 vs. 1,484 events, P<0.0001). Ventricular tachyarrhythmic events mainly occurred within the first 30 days after the threshold crossing event; however, a similar trend was not observed for the atrial tachyarrhythmic events.

Conclusions: Intrathoracic impedance monitoring may predict arrhythmic events, especially ventricular arrhythmias, in patients with HF and provides an additional management tool. (*Circ J* 2011; **75:** 2614–2620)

Key Words: Arrhythmia; Heart failure; Implantable cardioverter-defibrillator; Intrathoracic impedance

Several studies have suggested that intrathoracic impedance monitoring may be useful for the early detection of cardiac decompensation in patients with heart failure (HF).[1–9] Yu et al reported that the intrathoracic impedance correlated inversely with pulmonary capillary wedge pressure and net fluid loss in HF patients hospitalized for fluid overload.[1] Cardiac resynchronization therapy defibrillator (CRT-D) devices are now capable of monitoring intrathoracic impedance using a fluid index algorithm that can automatically alert the clinician or patient if the intrathoracic impedance decreases significantly. A decrease in intrathoracic impedance may primarily indicate pulmonary fluid accumulation because of cardiac decompensation. Furthermore, Catanzariti et al showed that a device-based algorithm facilitated the detection of HF deterioration and reduced the number of HF hospitalizations.[7]

Editorial p2539

Although intrathoracic impedance monitoring was developed to detect clinical deterioration of HF, its application for predicting the occurrence of arrhythmias has not been fully explored. The aim of this analysis was to evaluate the relationship between changes in intrathoracic impedance and the subsequent occurrence of cardiac arrhythmias.

Methods

Study Design

The study patient cohort was determined retrospectively from the Concerto-AT study,[10] an international, multicenter, pro-

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Table 1. RR Analysis of Arrhythmic Episodes

Parameter	All arrhythmias		Atrial arrhythmias		Ventricular arrhythmias	
	RR (95%CI)	P value	RR (95%CI)	P value	RR (95%CI)	P value
TC	1.87 (1.75–1.99)	<0.0001	2.01 (1.86–2.16)	<0.0001	1.55 (1.37–1.74)	<0.0001
Baseline NYHA	3.01 (2.78–3.26)	<0.0001	2.31 (2.09–2.55)	<0.0001	5.48 (4.79–6.28)	<0.0001
Sex	1.28 (1.20–1.36)	<0.0001	1.07 (0.99–1.15)	0.072	2.08 (1.86–2.34)	<0.0001
Age	1.00 (1.00–1.00)	<0.0001	1.01 (1.00–1.01)	0.002	1.00 (1.00–1.01)	0.142

RR, relative risk; CI, confidence interval; TC, threshold crossing; NYHA, New York Heart Association.

spective, non-randomized clinical trial evaluating the efficacy of atrial cardioversion in patients with chronic HF. A total of 282 patients from 41 institutions in the United States, Europe, and Japan who were successfully implanted with a CRT-D device (Concerto, Medtronic, Minneapolis, MN, USA) between January 27, 2006 and May 22, 2007 were included in this analysis. The detailed patient selection criteria have been previously described.[10] Briefly, patients were eligible if they had a standard indication for a CRT-D device, QRS duration ≥120 ms, New York Heart Association (NYHA) functional class III or IV HF, and left ventricular ejection fraction (LVEF) ≤35%, despite optimal medical therapy. Patients with permanent atrial fibrillation (AF) were excluded. All patients were required to meet all enrollment inclusion criteria, have no exclusion criteria, and provide written informed consent.

Intrathoracic Impedance Monitoring Algorithm

The CRT-D device used in the study had several additional diagnostic capabilities for HF management, including intrathoracic impedance monitoring. The details of the intrathoracic impedance monitoring and derived OptiVol fluid index algorithm used in the study device have been described in detail previously.[1,4,6] In brief, intrathoracic impedance was calculated once daily as an average of 64 impedance measurements between the right ventricular defibrillation lead coil and the CRT-D device can, which was measured every 20 min from 12 PM to 5 PM, the best time of day to observe a fluid overload condition, in order to minimize the effects of respiration and posture on impedance. The daily impedance was compared with a reference, which tracked the trends in the preceding daily impedance values. The cumulative difference between the daily and reference impedances was used to calculate the OptiVol fluid index. The device was programmed to store the data if the fluid index increased above a programmed threshold, nominally set at 60 ohm-days, which came from the results of a previous study.[1] The fluid index was inactive for the first 34 days after device implantation to allow for 30 days of post-implant pocket healing and 4 days to draw the reference impedance.

Device Programming and Definitions

Baseline device programming including arrhythmic event detection and treatment was at the discretion of the implanting physician. A full interrogation of the CRT-D device was performed at each visit. Arrhythmic events implied there were either atrial or ventricular tachyarrhythmias. Atrial tachyarrhythmias included atrial tachycardia (AT), atrial flutter (AFL), and AF. Sustained ventricular tachycardia (VT) or fibrillation (VF) was considered a ventricular tachyarrhythmic event. Non-sustained or self-terminating VT was excluded from the analysis. Arrhythmic events that occurred within the first 34 days after the implant procedure were excluded from the analysis because the thoracic impedance fluid index had not been established. The study patients were classified into 2 groups: with and without OptiVol fluid index threshold crossings. Patient follow-up occurred at 1, 3, 6, and 12 months post-device implantation.

Statistical Analysis

Baseline characteristics were compared between the patients with and without a fluid index crossing. Exploratory analyses, including a contingency table analysis and univariate regression, were conducted to evaluate the association between fluid index crossings and patients' baseline characteristics such as age, sex, and cardiac disease history. The Poisson regression method was then applied to investigate whether a fluid index threshold crossing was a predictor of arrhythmic events after adjustment for the patient's baseline characteristics.[11]

Results

Study Patients

The baseline characteristics of all the study patients were described in detail previously.[10] In brief, 71% were male, 93% had NYHA class III HF, 56% had ischemic cardiomyopathy, and the median age was 68.3 years. The mean QRS duration was 157.0±23.4 ms, and the mean LVEF was 23.3±6.8%. Baseline medications included angiotensin-converting inhibitors or angiotensin receptor blockers (87%), β-blockers (88%), and diuretics (85%). In terms of a history of arrhythmias, 112 patients (40%) had atrial arrhythmias, including AT, AFL, and AF, and 129 (46%) had ventricular arrhythmias, including sustained VT (18%) and VF (10%), at baseline. The mean follow-up duration was 10.0±3.2 months.

Arrhythmic Events

A total of 4,725 arrhythmic events occurred at least 34 days post-device implantation in 129 (46%) study patients, including 3,521 atrial events in 90 patients and 1,204 ventricular events in 70 patients. Ventricular arrhythmic events were successfully treated with antitachycardia pacing in 897 (74.5%) and direct current shock deliveries in 107 (8.9%) episodes; 200 (16.6%) ventricular events were not treated because the cycle lengths of most of those events were detected as only being in the MONITOR zone, which was programmed by each of the investigators.

In the regression analysis, the exploratory variables considered for the analysis were threshold crossing events, patient sex, age at device implantation, baseline NYHA functional class, LVEF, QRS duration, and ischemic vs. non-ischemic HF. As a result, the arrhythmic events were significantly associated with the occurrence of a fluid index threshold crossing, higher NYHA class at baseline, female sex, and age (Table 1). In particular, the occurrence of a fluid index threshold crossing and higher NYHA class at baseline were strongly associated with arrhythmic events during the follow-up period (relative

Table 2. Characteristics of TC (+) and TC (–) Groups at Enrolment

	TC (+) group* (n=145)	TC (–) group† (n=137)	P value
Male, n (%)	102 (70)	99 (72)	0.13
Age, years	68±12	66±11	0.23
NYHA functional class, n (%)			0.08
III	138 (95)	123 (90)	
IV	7 (5)	14 (10)	
QRS duration, ms	154.5±21.8	159.7±24.8	0.07
LVEF, %	22.8±6.8	23.7±6.8	0.30
Cause of heart failure, n (%)			0.18
Ischemic	88 (61)	70 (51)	
Non-ischemic	55 (38)	61 (45)	
Medications, n (%)			
ACE inhibitors or ARBs	123 (85)	121 (88)	0.39
Antiarrhythmic class I	9 (6)	4 (3)	0.26
Antiarrhythmic class III	35 (24)	32 (23)	0.88
β-blockers	127 (88)	121 (88)	0.85
Digitalis	50 (34)	58 (42)	0.18
Diuretics	119 (82)	122 (89)	0.10
Complete AV block, n (%)	9 (6)	12 (9)	0.41
Atrial tachyarrhythmias, n (%)	60 (41)	52 (38)	0.34
Ventricular tachyarrhythmias, n (%)	68 (47)	61 (45)	0.34

*Patients with TCs of the fluid index; †Patients with no TCs of the fluid index.
LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; AV, atrioventricular. Other abbreviations see in Table 1.

Table 3. Relationship Between TC Episodes and Arrhythmic Events

	TC (+) group (n=145)*		TC (–) group (n=137)†		P value‡
	Episode	Patient	Episode	Patient	
VT/VF	753	36	451	34	0.002
AT/AF	2,488	52	1,033	38	<0.0001
Total	3,241	70	1,484	59	<0.0001

*Patients who had TCs of the fluid index; †patients who had no TCs of the fluid index; ‡P values were compared between the 2 groups using the number of episodes.
VT, ventricular tachycardia; VF, ventricular fibrillation; AT, atrial tachycardia; AF, atrial fibrillation. Other abbreviation see in Table 1.

risk (RR) 1.87, 95% confidence interval (CI) 1.75–1.99, P< 0.0001; and RR 3.01, 95%CI 2.78–3.26, P<0.0001, respectively). A fluid index threshold crossing and higher NYHA class at baseline were also strongly associated with atrial arrhythmic events (RR 2.01, 95%CI 1.86–2.16, P<0.0001; and RR 2.31, 95%CI 2.09–2.55, P<0.0001, respectively). The multiple regression analysis also suggested that a higher NYHA class at baseline was a risk factor for ventricular arrhythmias (RR 5.48, 95%CI 4.79–6.28, P<0.0001). Patients with fluid index threshold crossing events were 1.55-fold as likely to have ventricular events (RR 1.55, 95%CI 1.37–1.74, P<0.0001) as those without crossing events.

Association Between Intrathoracic Impedance and Arrhythmias

All 282 eligible study participants were grouped into 2 analysis cohorts: patients with at least 1 fluid index threshold crossing (TC (+) group, n=145) and those without a fluid index threshold crossing (TC (–) group, n=137). There were no significant differences between the 2 groups in the baseline characteristics (Table 2). Arrhythmic events in the TC (+) group occurred significantly more frequently than that in the TC (–) group (P<0.0001) (Table 3). Moreover, a statistically significant association was observed between fluid index threshold crossings and both atrial and ventricular arrhythmic events.

Time Course of Arrhythmic Events

In order to determine if intrathoracic impedance monitoring could be used as an indicator of the occurrence of arrhythmic events, the temporal relationship between the fluid index threshold crossings and subsequent arrhythmic events was investigated. Of the TC (+) group patients, 70 (48%) had at least 1 arrhythmic event during the follow-up period. Moreover, 45 of the TC (+) patients experienced arrhythmic events after a threshold crossing. Ventricular arrhythmic events occurred after a threshold crossing in 23 patients (16%) in the TC (+) group (Figure 1). An analysis of the time course of those ventricular arrhythmic events showed that a significantly greater proportion of ventricular arrhythmic events occurred within 1 month of a fluid index threshold crossing than occurred at least 1 month after a fluid index threshold crossing (55.8% vs. 44.2%, P=0.0359) (Figure 2). In contrast, the proportion of atrial arrhythmic events occurring at least 1 month following a threshold crossing was significantly higher than that occurring within 1 month of a fluid index threshold crossing (54.9% vs. 45.1%, P=0.0004) (Figure 3). In summary, ven-

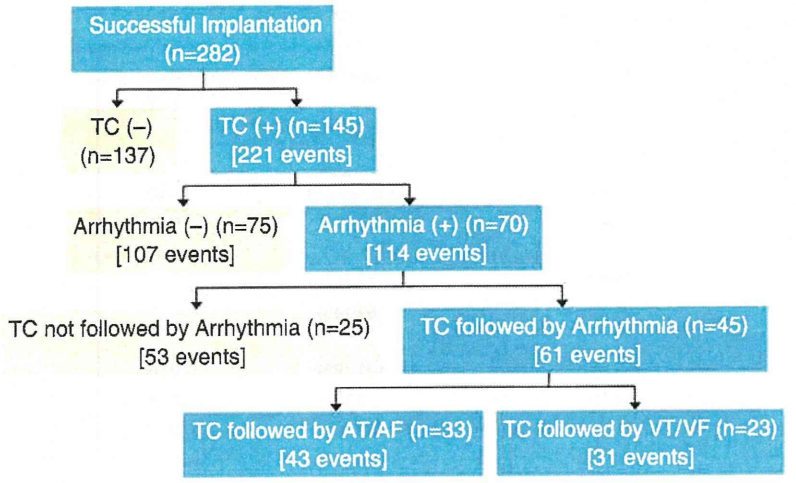

Figure 1. Event time assessment. Of 282 patients 145 (51%) had threshold crossing (TC) events. Atrial and ventricular arrhythmic events occurred after TCs in 33 and 23 TC(+) patients, respectively; 11 TC(+) patients experienced both atrial and ventricular arrhythmic events after TCs. AT, atrial tachycardia; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation.

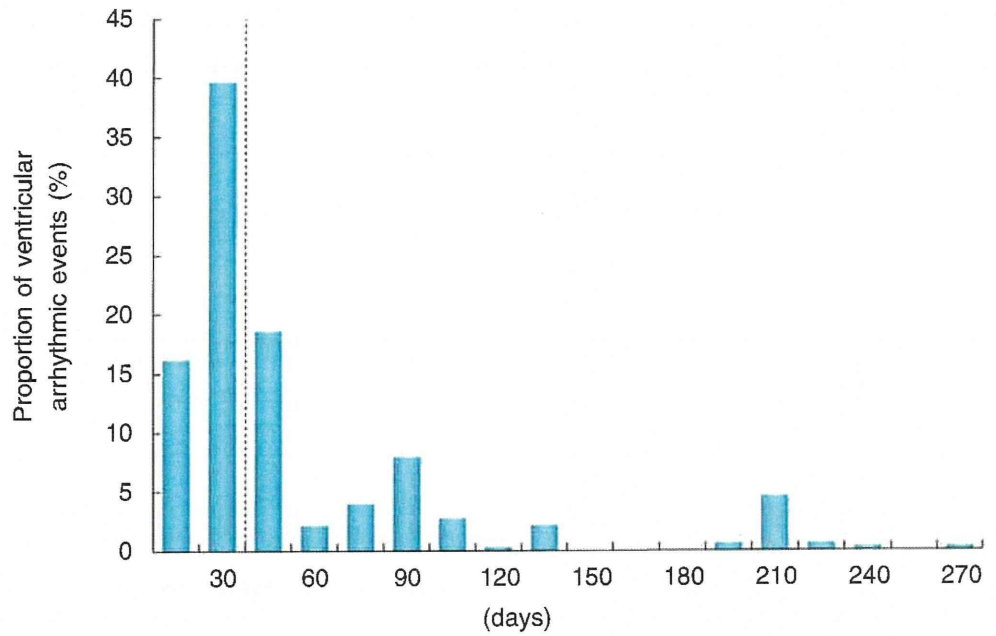

Figure 2. Relationship between the proportion of ventricular arrhythmic events after a fluid index threshold crossing (TC) and the period of time from the occurrence of the TC. The proportion of ventricular arrhythmic events within 1 month of a fluid index TC was significantly higher than that after 1 month (55.8% vs. 44.2%, P=0.0359).

tricular arrhythmic events were more likely to occur within 1 month after a threshold crossing. However, no such trend was observed for the atrial arrhythmic events.

Discussion

Sudden cardiac death is often associated with severe HF, presumably because of ventricular tachyarrhythmias.[12–14] The occurrence of ventricular arrhythmias may increase because of the existence of myocardial mechanoelectrical feedback[15,16] or the hemodynamic consequences of sympathoadrenergic hyperactivity,[17] concomitant with deteriorating HF. Similarly, the prevalence of atrial tachyarrhythmias, including AF, increases with the severity of HF.[18–22] HF results in changes to the atrium that predispose it to the development and maintenance of atrial arrhythmias.[23] Decreased atrial refractory periods, slowed atrial conduction, or increased heterogeneity during atrial repolarization can promote the development and maintenance of atrial arrhythmias.[24] Prior studies have focused their attention on intrathoracic impedance as an indicator of HF decompensation. However, consideration has also been given to additional applications of intrathoracic impedance monitoring in the man-

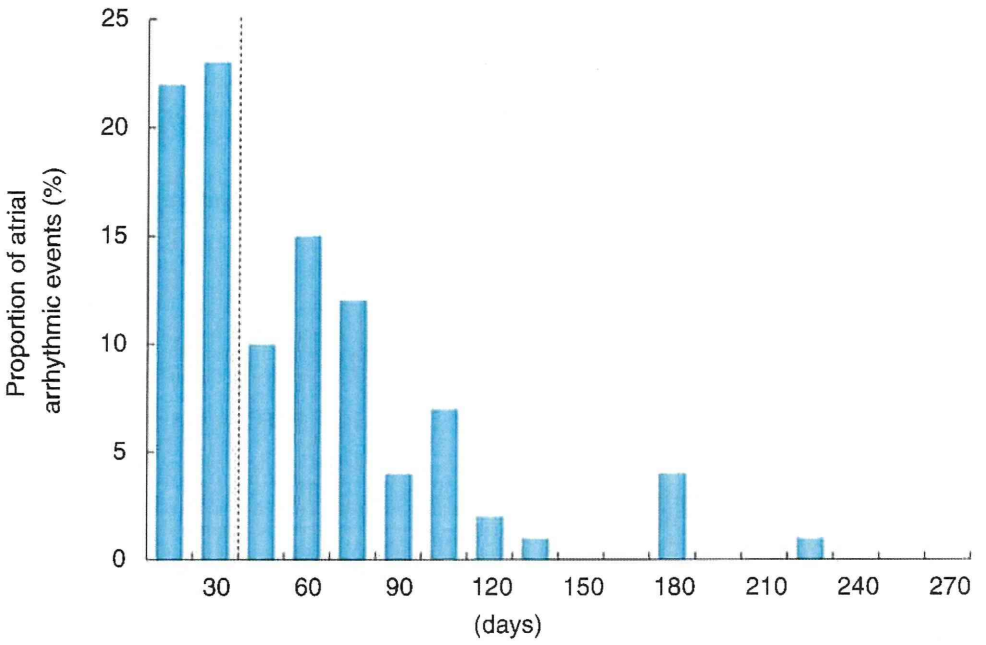

Figure 3. Relationship between the proportion of atrial arrhythmic events after a fluid index threshold crossing (TC) and the period of time from the occurrence of the TC. The proportion of atrial arrhythmic events after 1 month of the TC was significantly higher than that within 1 month (54.9% vs. 45.1%, P=0.0004).

agement of HF. Andriulli et al reported a case of repeated VT episodes preceded by an acutely lowered thoracic impedance recorded with a CRT-D device.[25] Moore et al reported that ventricular arrhythmic episodes were preceded by cumulative differences between the averaged daily and reference impedance on the dates leading up to the ventricular arrhythmic events, which was used as a diagnostic indicator rather than the OptiVol fluid index.[26] As for atrial arrhythmic events, Jhanjee et al reported that worsening pulmonary congestion evidenced by fluid index threshold crossings was associated with an increase in the frequency of atrial arrhythmias, and that those arrhythmias may be responsible for triggering episodic pulmonary congestion more often than previously suspected.[27]

Our retrospective observational study both confirmed and extended these findings by demonstrating a relationship between changes in intrathoracic impedance and the occurrence of cardiac arrhythmias within a large patient cohort. We investigated the temporal relationship between ventricular and atrial arrhythmic events and changes in intrathoracic impedance using the OptiVol fluid index. A multiple regression analysis revealed that both the occurrence of a fluid index threshold crossing and a higher NYHA class at baseline were independent predictors of atrial arrhythmic events, ventricular events, and the total number of arrhythmic events. Additionally, the patients with fluid index threshold crossings had significantly more atrial and ventricular arrhythmic events than those without threshold crossings during the follow-up period. These data suggest that cardiac arrhythmias are closely related to the fluid index threshold crossings, which in turn correlates with an increasing severity of HF. We, therefore, propose that changes in intrathoracic impedance can be regarded as a warning for cardiac arrhythmias, which tend to progress in parallel with exacerbation of HF.

Benefits of Early Warning of Cardiac Arrhythmias

Ventricular arrhythmic events sometimes result in the delivery of ICD shocks, which can be painful and increase the patient's anxiety. Additionally, Poole et al reported that the patients who received ICD shocks for arrhythmias had a substantially higher risk of death than similar patients who did not receive such shocks.[28] If changes in intrathoracic impedance can predict the occurrence of ventricular arrhythmias, effective early medical management may prevent the delivery of ICD shocks, resulting in a significant benefit to the patient.

Additional Considerations

The report by Moore et al[26] and our analysis suggest that the application of intrathoracic impedance monitoring as an indicator of the occurrence of ventricular arrhythmic events may lack specificity. Vollmann et al reported that the fluid index threshold crossing alert detected clinical HF deterioration with a 60% sensitivity (95%CI 46–73) and positive predictive value of 60% (95%CI 46–73) at the nominal threshold setting of 60 ohm-days.[5] Predicting the occurrence of an arrhythmia based on a cardiac overload that may result in HF cannot exceed the accuracy of predicting clinical HF deterioration using the intrathoracic impedance system. Furthermore, arrhythmias do not always appear at the time of HF deterioration. There also might be some prolonged cycle length ventricular events that are undetectable by the device programming, which induce cardiac deterioration and lead to a change in intrathoracic impedance. Thus, the observation that ventricular arrhythmias occurred after the threshold crossing in 16% of the TC(+) group patients in this study was reasonable and potentially clinically meaningful.

Although intrathoracic impedance measurements as currently implemented in implantable devices may not perform ideally

as an indicator of arrhythmic events, tailored use in combination with consideration of the patient's history and the impedance trend at the time of the event may be useful. However, the hypothesis that changes in intrathoracic impedance predict the occurrence of arrhythmias requires prospective validation.

Study Limitations

This retrospective study is subject to the limitations of all such studies. First, no randomization or blinding was applied. Second, all arrhythmic events used for the analysis were based on the device diagnosis and the programmed settings determined only by the physician's discretion. The atrial arrhythmia detection criteria of the device requires an atrioventricular conduction of 2:1 or greater for a minimum of 32 ventricular cycles. Atrial arrhythmic events are detected when the median atrial cycle length is less than a minimum value programmed by the physician. Helmut et al reported that the positive predictive values of atrial arrhythmic episodes were 95.3% and 95.7% for previous devices.[29] The ventricular arrhythmia detection algorithm operates to discriminate between supraventricular and ventricular tachyarrhythmias based on atrial and ventricular depolarization timing, ventricular cycle length regularity, AF criteria and far-field criteria.[30,31] Stadler et al demonstrated a positive predictive accuracy of 91.5% for the detection of ventricular arrhythmia episodes.[30] Third, the data for antitachycardia pacing episodes or direct current shock deliveries were not available for analysis in relation to the fluid index threshold crossings in this study. Finally, in regard to the fluid index setting, the nominal detection threshold value of 60 ohm-days used in this study demonstrated a 76.9% sensitivity in the large-scale observational study by Vollman et al.[5] However, some studies have reported that the positive predictive value of this proposed threshold for the OptiVol index related HF is relatively low.[1,4,32] Our data also showed that the fluid index threshold was crossed before atrial and ventricular arrhythmic events with a positive predictive value of 19% and 14%, respectively. The OptiVol index was developed to predict HF deterioration and may be affected by other events (eg, pneumonia, pleural effusion, pocket infection, drinking, etc). Ypenburg et al suggested that the nominal programmed fluid index threshold was not specific for the assessment of HF, and proposed that a threshold value of 120 ohm-days would provide a reasonable balance between sensitivity and specificity.[32] Further prospective studies in larger populations are needed to assess this hypothesis.

Conclusions

In this retrospective study of patients with NYHA class III and IV HF and who were implanted with CRT-D devices, arrhythmic events were associated with a dramatic change in the intrathoracic impedance-derived fluid index. Further prospective clinical trials are required to confirm the relationship between arrhythmic events and intrathoracic impedance monitoring, and to determine whether device-based fluid index monitoring can facilitate preemptive therapy to reduce the occurrence of arrhythmic events in patients with HF.

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Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II Study)

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Aims Atrial fibrillation (AF) is a common arrhythmia frequently associated with hypertension. This study was designed to test the hypothesis that lowering blood pressure by angiotensin II-receptor blockers (ARB) has more beneficial effects than by conventional calcium channel blockers (CCB) on the frequency of paroxysmal AF with hypertension.

Methods and results The Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II study) is an open-label randomized comparison between an ARB (candesartan) and a CCB (amlodipine) in the treatment of paroxysmal AF associated with hypertension. Using daily transtelephonic monitoring, we examined asymptomatic and symptomatic paroxysmal AF episodes during a maximum 1 year treatment. The primary endpoint was the difference in AF frequency between the pre-treatment period and the final month of the follow-up. The secondary endpoints included cardiovascular events, development of persistent AF, left atrial dimension, and quality-of-life (QOL). The study enrolled 318 patients (66 years, male/female 219/99, 158 in the ARB group and 160 in the CCB group) treated at 48 sites throughout Japan. At baseline, the frequency of AF episodes (days/month) was 3.8 $\pm$ 5.0 in the ARB group vs. 4.8 $\pm$ 6.3 in the CCB group (not significant). During the follow-up, blood pressure was significantly lower in the CCB group than in the ARB group ($P < 0.001$). The AF frequency decreased similarly in both groups, and there was no significant difference in the primary endpoint between the two groups. There were no significant differences between the two groups in the development of persistent AF, changes in left atrial dimension, occurrence of cardiovascular events, or changes in QOL.

Conclusions In patients with paroxysmal AF and hypertension, treatment of hypertension by candesartan did not have an advantage over amlodipine in the reduction in the frequency of paroxysmal AF (umin CTR C000000427).

Keywords Atrial fibrillation • Hypertension • Renin–angiotensin system • Candesartan • Amlodipine • Secondary prevention • Upstream therapy

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Introduction

Atrial fibrillation (AF) is a common arrhythmia associated with increased mortality and morbidity.[1–3] Antiarrhythmic drugs currently available have limited efficacy in the prevention of AF recurrence, and provide no substantial benefits in the prognosis of AF patients.[4,5] An approach emerging from the experimental evidence is the pharmacological modification of electrical and structural remodelling of atria. Certain neurohumoral elements, including the rennin–angiotensin system (RAS), have attracted the increased attention of cardiologists as the therapeutic target.[6–12] However, a recent large randomized trial, the GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation) study,[13] has demonstrated that treatment with valsartan was not associated with a reduction in the time to AF recurrence, making the issue more controversial.

More than half of AF patients are known to have hypertension as a co-morbid condition,[14,15] and we frequently encounter a clinical question: Which anti-hypertensive drug should be selected for lowering blood pressure (BP) in patients with AF and hypertension? This question proves to be particularly annoying in the treatment of hypertension with frequent paroxysmal AF. We conducted the J-RHYTHM II study[16] to assess the potential benefit of BP control by RAS inhibition with candesartan in patients with both hypertension and paroxysmal AF when compared with that by the conventional calcium channel blocker (CCB), amlodipine.

Methods

Study design

The rationale and the design of this study have been described previously.[16] The J-RHYTHM II study was a prospective, multicentre, randomized, and open-label trial. It was designed and supervised by the Japanese Society of Electrocardiology, and financially supported by the Japanese Heart Foundation. The study protocol was approved by the ethics committee at each participating hospital.

Patients

Patients entering this study needed to meet both of the following criteria: (i) a history of paroxysmal AF within 6 months, and (ii) hypertension, defined as a systolic BP $\geq$140 mmHg and/or a diastolic BP $\geq$90 mmHg, or requiring any hypertension treatment at enrolment. Paroxysmal AF should be an episode with spontaneous termination within 7 days, which was demonstrated on electrocardiograms (ECG) taken within 6 months before enrolment. The exclusion criteria were (i) a history of angina pectoris, (ii) persistent AF with a duration longer than 1 week and permanent AF, (iii) AF that has occurred within 1 month from the onset of myocardial infarction, (iv) transient AF associated with cardiac surgery, (v) contraindication for anticoagulation therapy, (vi) pregnancy or the possibility of pregnancy, and breast feeding, (vii) patient age of 18 or under, and (viii) a judgment by the attending physician that patient participation would be inappropriate. All patients had to have been on a stable regimen of treatment for paroxysmal AF and for any underlying cardiovascular disorders for at least 1 month prior to enrolment. Patients were allowed to continue all previously prescribed treatments and had to provide written informed consent before enrolment.

Observation period, randomization, and treatment

During the first month (4 weeks) after enrolment, the treatment of AF and hypertension was continued without any changes from that prior to entering the study in order to evaluate the baseline data of the patient, including echocardiography and quality-of-life (QOL) assessment by AF-specific QOL questionnaires (AFQLQ).[17] Each patient was provided with a transtelephonic monitoring (TTM) device and was requested to transmit ECG records (for 30 s at least once a day at a predetermined time) and any arrhythmia-related symptoms every day to a central service under contract for the study (Nihon Kohden, Tokyo).

After this 1 month observation period, the patients were randomly assigned to either a candesartan or an amlodipine group by means of a computerized randomization system based on stratification according to age, sex, BP during the observation period, existence of structural heart diseases and regular use of any antiarrhythmic drugs. After randomization, the assigned therapy was initiated in an open-label fashion and continued throughout the whole follow-up period for a maximum of 12 months.

In the candesartan group, candesartan was prescribed with an initial dose of 4–8 mg/day (maximal dose 12 mg/day), and the use of any dihydropiridine CCB or RAS inhibitors other than candesartan was prohibited during the study. In the amlodipine group, amlodipine was prescribed with an initial dose of 2.5 mg/day (maximal dose 5 mg/day), and the use of any RAS inhibitors or CCB other than amlodipine was prohibited. The target BP was set at 130/85 mmHg in both groups. When the BP did not reach the target level irrespective of the maximal dose of the assigned drug, other anti-hypertensive drugs including diuretics, β-blockers and α-blockers could be used. Antithrombotic therapy was to be continued during the study according to the Japanese Guidelines. Antiarrhythmic drugs available were limited to several class I drugs (disopyramide, procainamide, quinidine, aprindine, pilsicainide, propafenone, and cibenzoline), and the attending physicians could select or change according to their clinical judgment for each patient.

During follow-up, the attending physicians were also to record BP every month, and the patients were requested to send daily and symptom-driven TTM. The dosages and kinds of all the anti-hypertensive drugs and antiarrhythmic drugs used during this period were recorded for each patient. Echocardiography and AFQLQ assessment were performed at the end of the follow-up period.

Endpoints

The primary endpoint was the difference in the frequency (days/month) of AF (symptomatic and asymptomatic) recorded on TTM between the observation period and the final month of the follow-up. The secondary endpoints were (i) cardiovascular events, which included cardiac death, myocardial infarction, cerebral infarction, and congestive heart failure or major bleeding requiring hospitalization, (ii) the progression of paroxysmal AF into persistent AF lasting for longer than 7 days, and/or requiring electrical conversion, (iii) left atrial dimension in echocardiography, and (iv) QOL assessed by the AFQLQ.

Statistical analysis

The estimated sample size was based on our estimate of the primary endpoint difference that the frequency of paroxysmal AF is to be lower by 25% in the candesartan group than in the amlodipine group. For a study to have 80% power to detect this difference, there would have to be 240 cases (120 per group) analysed. Our

target sample size of 376 patients (188 per group) was drawn by adjusting for our estimates of losses through the follow-up being 20% and data loss due to technical errors in sending TTM being 20%.

The primary analysis was the difference between the two groups in the number of days with TTM-recorded AF, which was an unadjusted intention-to-treat comparison using the unpaired Student's *t*-test. Transtelephonic monitoring was overviewed and diagnosed in a blind manner by a TTM diagnosis committee. For each month, patients with uninterpretable ECG on TTM due to artefacts were excluded from the analysis. Inter-group differences in the occurrence of cardiovascular events and development of persistent AF were analysed by the χ^2 test. Inter-group differences in left atrial dimension were assayed by the unpaired Student's *t*-test. Differences between groups and over time in the absolute values of BP were investigated by repeated ANOVA. Secondary endpoint questionnaire results were collected for each group, and any changes from the baseline value were compared between groups by the unpaired Student's *t*-test. Patient background factors and other observation items were aggregated by group, and any inter-group differences were analysed by methods corresponding to the nature of the data. Data were expressed as mean ± SD, and statistical significance was set at $P < 0.05$.

Role of the funding source

The funding source had no role in the study design, data collection, analysis and interpretation, or the writing of the report.

Results

Patients and follow-up

From September 2006 through August 2008, 326 patients were enrolled at 48 centres throughout Japan; 8 patients withdrew their consent during the observation period. Subsequently, 318 patients were randomized; 158 were assigned to a candesartan group, and 160 to an amlodipine group. This sample size was more than that necessary for the prespecified statistical analysis ($n = 240$). Baseline clinical characteristics of the patients are shown in *Table 1*. The mean age was 69 years old and 69% of the patients were male. A total of 76.7% of the patients had received anti-hypertensive drugs, and 70.4% antiarrhythmic drugs. History of prior embolism, heart failure, and diabetes mellitus was observed in 7.6, 2.5, and 9.1%, respectively. The mean left ventricular ejection fraction was 67.6%, and slightly but significantly greater in the candesartan than in the amlodipine group. Mean left atrial dimension was 39.1 mm and was not significantly different between the groups.

The frequency of all paroxysmal AF (both symptomatic and asymptomatic) recorded on TTM during the observation period was 3.8 ± 5.0 days/month in the candesartan group and 4.8 ± 6.3 days/month in the amlodipine group ($P = 0.116$). Less than half of the AF episodes were symptomatic; the frequency of symptomatic AF was 1.4 ± 3.0 in the candesartan group and 1.4 ± 2.9 in the amlodipine group ($P = 0.903$).

Test drug dosage and concomitant cardiovascular therapies in the initial treatment period are shown in *Table 1*. The mean dose of the test drug was 8.0 ± 2.7 mg/day in the candesartan group and 4.3 ± 1.7 mg/day in the amlodipine group. Beta-blockers, antiplatelet agents, and anticoagulant agents were used in 30.8, 29.6, and 52.8% of the patients, respectively, and there were no significant differences between the two groups. Diuretics were more frequently used in the candesartan group than in the amlodipine group (12.7% vs. 5.6%, $P = 0.029$). Angiotensin-converting enzyme (ACE)-inhibitors were not used throughout the study in the both groups. The rate of antiarrhythmic drug usage tended to be higher in the amlodipine group than the candesartan group not only in the baseline (*Table 1*), but also throughout the follow-up period (final month: 72.5 vs. 68.2%, $P = 0.447$), although the difference did not reach a statistical significance.

Systolic BP during the observation period was 140.7 ± 15.5 mmHg in the candesartan group and 139.4 ± 15.4 mmHg in the amlodipine group ($P = 0.486$). *Figure 1* shows the time-course of BP during the follow-up period. Systolic and diastolic BPs decreased gradually during the study in both groups, but the extent of BP reduction with amlodipine was significantly greater than that with candesartan ($P < 0.0001$ by repeated ANOVA).

Primary endpoint

At the last month of the follow-up, the frequency of total AF was 2.1 ± 3.8 days/month in the candesartan group ($n = 149$) and 2.4 ± 4.4 days/month in the amlodipine group ($n = 155$, $P = 0.512$). The frequency of symptomatic AF was 1.0 ± 3.1 days/month in the candesartan and 0.8 ± 2.6 days/month in the amlodipine group ($P = 0.544$). *Figure 2A* shows the primary endpoint (the difference in the frequency of AF between the observation period and the final month of the follow-up); there was no significant difference between the two groups ($P = 0.351$). The two groups showed similar gradual decreases in the frequencies of both total and symptomatic AF during the whole follow-up period (*Figure 2B*). In the both candesartan and amlodipine groups, there was a significant decrease in the total AF days from the baseline to the final follow-up month (candesartan $P = 0.002$, amlodipine $P = 0.0002$); a tendency of reduction was also observed in the symptomatic AF days from the baseline to the final follow-up month, although the reduction did not reach a statistical significance (candesartan $P = 0.15$, amlodipine $P = 0.07$).

Secondary endpoints and *post hoc* analyses

Table 2 summarizes the secondary endpoints in this study. There were no significant differences in these endpoints between the two groups. Cardiovascular events tended to occur more frequently in the amlodipine than in the candesartan group, but the difference did not reach statistical significance. The development of persistent AF (lasting >7 days or requiring electrical cardioversion) tended to be more frequent in the amlodipine group (15%) than in the candesartan group (8.2%), but the difference was not statistically significant. The differences in QOL represented by AFQLQ between the observation period and the final follow-up were similar in the two groups in all of the AFQLQ subsets.

Because the two groups showed significant differences in BP reduction during the follow-up period (*Figure 1*), *post hoc* analyses were performed to examine the influence of systolic BP on the primary endpoint. The patients were divided into three groups according to their systolic BP at the final follow-up: a lower group (≤126 mmHg, $n = 108$), a middle group (126–139 mmHg,

Table 1 Baseline characteristics

Characteristics	Candesartan (n = 158)	Amlodipine (n = 160)	P-value
Age (years)	66.0 ± 9.7	65.1 ± 9.3	0.429
Male (%)	109 (69.0)	110 (68.8)	0.905
SBP (mmHg)	139.5 ± 15.4	140.7 ± 15.5	0.486
DBP (mmHg)	81.0 ± 11.3	82.5 ± 11.2	0.256
Heart rate (bpm)	70.9 ± 14.4	69.5 ± 13.9	0.379
Duration of AF			0.818
<1 year	41 (25.9)	37 (23.1)	
≤1, <5 years	57 (36.1)	66 (41.3)	
≥5 years	43 (27.2)	41 (25.6)	
Unknown	17 (10.8)	16 (10)	
Coexisting conditions			
Prior embolism (%)	12 (7.6)	12 (7.5)	1.000
Heart failure (%)	4 (2.5)	4 (2.5)	1.000
Myocardial infarction (%)	3 (1.9)	1 (0.6)	0.370
Angina pectoris (%)	3 (1.9)	4 (2.5)	1.000
Cardiomyopathy (%)	4 (2.5)	3 (1.9)	0.690
Valvular disease (%)	9 (5.7)	14 (8.8)	0.387
Diabetes (%)	15 (9.5)	14 (8.8)	0.848
Hyperlipidaemia (%)	47 (29.7)	47 (29.4)	1.000
Echocardiograms			
LVDd	47.5 ± 4.9	47.87 ± 4.9	0.549
LVEF	69.1 ± 8.1	66.2 ± 8.2	0.003
LAD	38.9 ± 6.7	39.3 ± 6.8	0.618
Treatment at baseline			
Anti-hypertensive therapy (%)	120 (75.9)	124 (77.5)	0.791
AAD (%)	105 (66.5)	119 (74.4)	0.141
PAF frequency during observation period			
Total PAF (days/month)	3.8 ± 5.0	4.8 ± 6.3	0.116
Symptomatic PAF	1.4 ± 3.0	1.4 ± 2.9	0.903
Treatment at initial follow-up			
Candesartan	8.0 ± 2.7 mg/day	—	—
Amlodipine	—	4.3 ± 1.7 mg/day	—
Diuretics (%)	20 (12.7)	9 (5.6)	0.029
β-Blockers (%)	48 (30.4)	50 (31.3)	0.867
Antiplatelet therapy (%)	46 (29.1)	48 (30.0)	0.863
Anticoagulant therapy (%)	80 (50.6)	88 (55.0)	0.435
Statins (%)	26 (16.5)	24 (15.0)	0.721

Data represent mean ± SD or frequency. SBP, systolic blood pressure; DBP, diastolic blood pressure; PAF, paroxysmal atrial fibrillation; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AAD, antiarrhythmic drug; bpm, beat per minute. Anti-hypertensive therapy includes ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers, β-blockers, α-blockers, and diuretics.

n = 95), and a higher group (≥139 mmHg, n = 105). There were no significant differences between the two groups in the reduction in AF frequency during the follow-up period in any subset analysis (*Table 3*).

Discussion

In the present J-RHYTHM II study, we tested a hypothesis that, in patients with paroxysmal AF associated with hypertension, candesartan may exert beneficial effect on the frequency of paroxysmal AF when compared with conventional hypertension therapy with amlodipine. In our study population, we could not find any differences between the two therapies in the nature of paroxysmal AF during the maximal follow-up of 1 year. These results were essentially unaffected by subgroup analyses depending on the systolic BP attained by the therapies. Our findings, in concordance with a recent GISSI-AF study,[13] do not support the concept that the blockade of RAS may have a favourable effect on the occurrence of AF beyond the control of BP.

There is considerable experimental evidence suggesting that the administration of angiotensin II-receptor blockers (ARB) may prevent or reverse the progression of atrial fibrosis in association

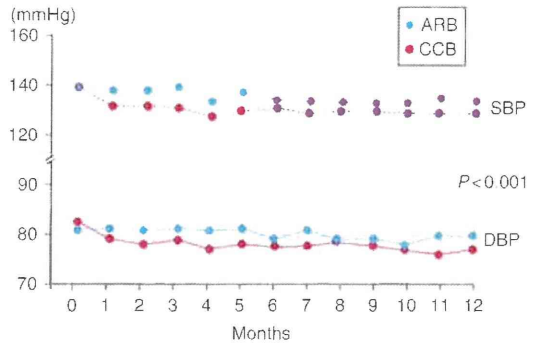

Figure 1 The time-course of systolic blood pressure and diastolic blood pressure in the candesartan (angiotensin II-receptor blocker) and amlodipine (calcium channel blocker) group. There were significant differences both in systolic and diastolic blood pressure between the groups ($P < 0.0001$ by ANOVA).

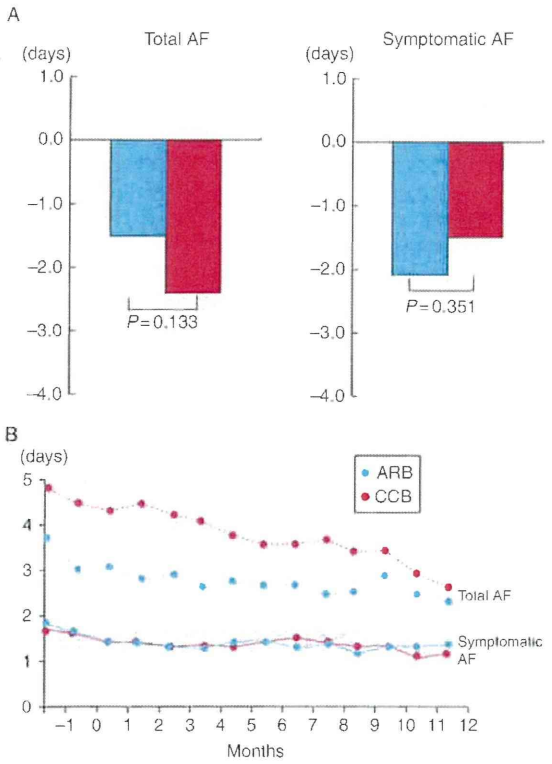

Figure 2 (*A*) Difference in the frequency of atrial fibrillation (days/month) between the observation period and the final month of the follow-up (Left: Total atrial fibrillation, Right: Symptomatic atrial fibrillation). Both in the candesartan (angiotensin II-receptor blocker) and amlodipine (calcium channel blocker) groups, the atrial fibrillation days decreased, but there were no significant differences between the two groups. (*B*) The time-course of the frequency (days/month) of total atrial fibrillation (dotted lines) and symptomatic atrial fibrillation (solid lines).

Table 2 Secondary endpoints

	Candesartan (n = 158)	Amlodipine (n = 160)	P-value
Cardiovascular events (%)			
Cardiovascular death	0 (0.0)	0 (0.0)	—
Acute myocardial infarction	0 (0.0)	0 (0.0)	—
Stroke	0 (0.0)	3 (1.8)	0.084
Major bleeding	0 (0.0)	1 (0.6)	0.320
Heart failure	0 (0.0)	0 (0.0)	—
Development of persistent AF	13 (8.2)	24 (15.0)	0.080
Changes in LAD	+0.34 ± 5.8	+0.25 ± 4.9	0.895
Changes in QOL assessment			
AFQLQ1	+0.9 ± 5.6	+1.8 ± 6.0	0.246
AFQLQ2	+1.5 ± 3.8	+2.2 ± 4.2	0.189
AFQLQ3	+1.6 ± 7.4	+2.6 ± 10.0	0.412

Data represent mean ± SD or frequency. AFQLQ1, frequency of symptoms; AFQLQ2, severity of symptoms; AFQLQ3, limitations of daily activities and mental anxiety (higher is better in these components).

Table 3 Frequency of paroxysmal atrial fibrillation in three tertiles of systolic blood pressure

	Candesartan	Amlodipine	P-value
Lower group			
Baseline (day/month)	3.5 ± 3.6 (49)	5.4 ± 6.8 (59)	0.081
Final follow-up	1.7 ± 2.7 (48)	3.1 ± 4.9 (58)	0.089
Difference	−1.6 ± 4.4 (48)	−2.4 ± 7.5 (58)	0.493
Middle group			
Baseline	3.5 ± 5.7 (42)	4.8 ± 6.5 (52)	0.306
Final follow-up	2.6 ± 5.4 (41)	2.7 ± 5.3 (51)	0.928
Difference	−1.0 ± 4.8 (41)	−2.2 ± 5.5 (51)	0.260
Higher group			
Baseline	3.9 ± 4.6 (61)	3.9 ± 5.2 (43)	0.936
Final follow-up	2.1 ± 3.3 (57)	1.3 ± 2.4 (44)	0.164
Difference	−1.7 ± 3.8 (57)	−2.6 ± 4.2 (43)	0.265

Data represent mean ± SD. ( ), number of patients.

with AF.[18–20] Actually, a series of clinical studies also showed that RAS inhibition had beneficial effects on the recurrence and perpetuation of AF.[21–23] On the contrary, however, *post hoc* analyses of the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) and CTAF (Canadian Trial of Atrial Fibrillation) studies could not find any beneficial effects of RAS inhibition on AF recurrence,[24,25] making it controversial that the experimental concept can be applied to clinical practice.

Recently, the first prospective randomized control trial, the GISSI-AF study,[13] challenged this issue. The trial enrolled all types of AF, evaluated the antiarrhythmic efficacy of valsartan

when compared with a placebo in a double-blind manner, and has demonstrated that valsartan was not associated with any beneficial effects on AF recurrence. Also, the results were consistent in any subgroups according to age, presence of heart failure, and usage of ACE-inhibitors, beta-blockers and antiarrhythmic drugs.[13]

The present J-RHYTHM II study focused upon a specific proportion of patients in the GISSI-AF study, patients with frequent paroxysmal AF associated with hypertension, in order to answer a question regarding which type of drug, ARB or CCB, is more favourable as an anti-hypertensive therapy for these patients. The primary endpoint was also somewhat different from the GISSI-AF study. We focused on the frequency of paroxysmal AF, while the GISSI-AF trial evaluated the time to a first recurrence of AF. Our study, using every-day TTM recordings, has revealed that anti-hypertensive therapy with candesartan has no significant advantage over amlodipine in the reduction in the frequency of paroxysmal AF. These results would strengthen the evidence from the GISSI-AF study.

In our secondary endpoint analysis, ~12% of the patients showed progression into persistent AF. This figure is consistent with a recent study[26] that revealed the rate of progression of paroxysmal into persistent AF in a variety of paroxysmal AF patients and identified hypertension as one of the potent risk factors for AF perpetuation. In the present study, we ascertained the similar progression rate in hypertensive patients with the use of daily TTM recordings and also found that the rate was not significantly affected by the administration of candesartan in a sample size of >300 patients. The changes in the left atrial dimension were also similar between the groups, which would be consistent with this result on AF perpetuation. The present results of the AF-specific QOL assessment are also plausible, because the frequency and perpetuation of AF was similar between the groups.

In our study, the incidence of thrombo-embolic events tended to be higher in the amlodipine than in the candesartan group. This might be inconsistent with the GISSI-AF study,[13] where strokes were more frequently observed in the valsartan group. However, we believe that our observation may have resulted from a by-chance occurrence due to the small number of patients studied.

Recently, several reports have been made on the relationships between anti-hypertensive drugs and AF primary prevention.[27–29] The effects of antihypertensive drugs on primary AF prevention might differ from drug to drug, but remain a matter of controversy. One of the difficult problems results from BP differences during long anti-hypertensive therapy.[30,31] Similarly, the present results could be influenced by the significant differences in BP between the two groups. However, the AF frequencies were not different between ARB and CCB in any of the subgroups divided according to the attained BP levels at the final follow-up; this *post hoc* analysis would suggest that the BP differences between the two groups were unlikely to play a major role in the results of the present study.

Limitations of our trial should include (i) it is an open-label trial, (ii) lack of a placebo arm, (iii) relatively higher rate of anti-arrhythmic drug usage in the amlodipine group, and (iv) a relatively short follow-up period. Although this was an open-label trial, the primary endpoint was blinded to the attending physicians and patients, and also to the TTM diagnosis committee, in order to minimize information biases. Because there was no placebo control group, we could not know the relationships between BP and the frequency of paroxysmal AF. The slightly higher rates of antiarrhythmic drug usage in the amlodipine group (the difference was statistically insignificant) might have affected the present results. Moreover, our results should be applied to a short-term follow-up of the patients.

In conclusion, under the conditions of the study and with statistical limitations, there were no differences in the frequency or perpetuation of paroxysmal AF with hypertension between anti-hypertensive therapies using candesartan and amlodipine. These data suggest that, for both patients and health-care providers, selection of anti-hypertensive drugs could be individualized from other patient characteristics.

Conflict of interest: none declared.

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Appendix 1

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Appendix 2

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Transmural and apicobasal gradients in repolarization contribute to T-wave genesis in human surface ECG

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Okada J, Washio T, Maehara A, Momomura S, Sugiura S, Hisada T. Transmural and apicobasal gradients in repolarization contribute to T-wave genesis in human surface ECG. *Am J Physiol Heart Circ Physiol* 301: H200–H208, 2011. First published April 1, 2011; doi:10.1152/ajpheart.01241.2010.—The cellular basis of the T-wave morphology of surface ECG remains controversial in clinical cardiology. We examined the effect of action potential duration (APD) distribution on T-wave morphology using a realistic model of the human ventricle and torso. We developed a finite-element model of the ventricle consisting of ~26 million elements, including the conduction system, each implemented with the ion current model of cardiomyocytes. This model was embedded in a torso model with distinct organ structures to obtain the standard ECG leads. The APD distribution was changed in the transmural direction by locating the M cells in either the endocardial or epicardial region. We also introduced apicobasal gradients by modifying the ion channel parameters. Both the transmural gradient (with M cells on the endocardial side) and the apicobasal gradient produced positive T waves, although a very large gradient was required for the apicobasal gradient. By contrast, T waves obtained with the transmural gradient were highly symmetric and, therefore, did not represent the true physiological state. Only combination of the transmural and the moderate apicobasal gradients produced physiological T waves in surface ECG. Positive T waves in surface ECG mainly originated from the transmural distribution of APD with M cells on the endocardial side, although the apicobasal gradient was also required to attain the physiological waveform.

electrocardiogram; computer simulation; T wave; body surface map; M cells

DESPITE ITS LONG HISTORY AND worldwide use in clinical cardiology for the diagnosis of various heart diseases, the cellular origin of the ECG waveform is not fully established. In particular, the genesis of the T wave remains controversial, largely because of its implication in arrhythmogenesis (1, 4, 20, 22). The T wave was originally considered to result from the heterogeneity of repolarization of the ventricle in the apicobasal direction (19). However, more recently, the transmural difference (gradient) of repolarization is considered important, as supported by the discovery of M cells isolated from the canine ventricular wall (2, 32). M cells are distributed in the deep subendocardium in the anterior wall, but are shifted to the deep subepicardium in the posterior wall, and are characterized by a longer action potential duration (APD) compared with the epicardial and endocardial myocytes, creating a significant gradient (1). Subsequent studies identified similar type of cells in guinea pig, rabbit, pig, and human ventricular tissues (8, 33, 35, 51).

However, when measurements are made in more intact preparations, there is accumulating evidence that the APD of M cells becomes shorter, resulting in smaller transmural dispersion (23). For instance, measurement of the human ventricles during cardiac surgery, rather than isolated cells or a ventricular wedge, produced no significant transmural heterogeneity of repolarization (42). The electronic cancellation effect introduced by intercellular coupling through gap junctions is considered the cause of these observations in intact preparations (5, 41), although experimental artifact has also been suggested (1). During surgery or in animal experiments, subjects receive anesthetic agents that may block sodium and/or delayed rectifier potassium currents, causing preferential shortening of the APD of M cells (31). Furthermore, the plunge electrode technique used in many studies may not necessarily probe the whole area and depth of the ventricular wall (42, 48). In a recent study, optical mapping revealed the distribution of APD in human ventricular tissue (12); however, only the posterior wall wedge was examined.

Computer simulation is widely used for studying cardiac electrophysiology and allows detailed analysis of the normal and abnormal electrical activity of the heart (18, 34, 46, 47). Although computer simulation does not provide conclusive data on actual tissue, if carefully designed, it can provide important supporting information. In the present study, we used this strategy to examine which pattern of APD distribution generated the normal waveform of the human surface ECG. We previously reported our detailed model of the human ventricles based on the human ventricular model of electrophysiology (44, 45). We embedded this model into a torso with the organ structures model and varied the distributions of M cells and APD, according to experimental data, to calculate the surface ECG. We found that both the apicobasal and transmural distribution of APD significantly influence the human T-wave morphology.

MATERIALS AND METHODS

Human heart and torso model. The details of this model were previously reported (50). We used a realistic model of the human heart with a conduction system embedded into the torso model based on the voxel-based, finite-element method. To save computational cost for such a large-scale model, we used composite mesh composed of fine mesh (0.2 mm) for the heart and the coarse mesh (1.6 mm) for the torso regions and solved it using the multilevel solution technique. The study protocol was approved by the Institutional Ethics Committee, and informed consent was obtained for the use of CT scan data.

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Heart model. The geometry of the three-dimensional voxel human heart model (mesh size 0.2 mm) was based on the multidetector computerized tomography data of the subject without cardiac dysfunction (Fig. 1*A*). We only analyzed the ventricles, although the total number of elements covering the heart region was equal to 244,187,136. We mapped previously reported human data on the spatial orientation of the myocyte (fiber orientation) to our model (http://gforge.icm.jhu.edu/gf/project/dtmri_data_sets/) (Fig. 1*B*).

To each voxel element, we implemented the previously reported ionic current model of human ventricular myocytes (45), and the propagation of excitation was modeled as a continuous system using the bidomain formulation (see supplemental material for details; the online version of this article contains supplemental data) (14). Anisotropy of action potential propagation was introduced by setting the conductivity in the longitudinal (fiber) direction larger compared with the transverse direction. We used the following values (Supplemental Table S1), according to the previous report (15).

Conduction system. The conduction system is indispensable for the analysis of ECG. We modeled the conduction system by one-dimensional elements based on Tawara's monograph (43), as shown in Fig. 2*A*. The electrophysiological properties were reproduced by the cell model proposed by Stewart et al. (36). The network of the conduction system consists of the free-running (insulated) part connecting the atrioventricular node to the sites of earliest activation and the network spreading from these sites along the endocardial surface. At each terminal, this network is connected to the voxel mesh node, representing the myocardial tissue, and from there the excitation propagates concentrically. Although the description by Tawara is qualitative, the current model can be validated by the agreement of simulation results of previously reported isochronal maps (Fig. 2, *B* and *C*) (9) and body surface voltage maps (Fig. 2*D*) (6, 40). In the simulation, we applied a small current to the root of the conduction system to initiate activation of the ventricles.

Torso model. The morphology of the voxel torso model was based on the computerized tomography data (Fig. 1*C*). Each organ was segmented manually (Fig. 1*D*), and specific conductivity (Supplemental Table S1) was assigned as previously reported (3, 21). Only the conductivity of the body surface (skin) was adjusted to obtain the physiological amplitude of ECG without changing its morphology. With a 1.6-mm element size, the total number of elements covering the torso was 40,038,400. In contrast to the heart tissue, the torso domain can be viewed as a passive conductor. Therefore, the potential ϕ^T satisfies the generalized Laplace equation

$$\frac{\partial}{\partial x_i}\left(G_{ij}^T \frac{\partial \phi^T}{\partial x_j}\right) = 0$$

where G_{ij}^T is the conductivity tensor.

APD distribution. We altered the APD distributions (gradients) in transmural and apicobasal (longitudinal) directions to determine the effects on ECG. Using the Ten Tusscher model (45), we found that the endocardial cells, M cells, and epicardial cells were modeled by adjusting the transient outward K^+ and the slow component of delayed rectifier K^+ currents (I_{Ks}). Transmural gradient was created by locating M cells in either the endocardial or epicardial sides (10–40%, Fig. 3*A*, or 60–90%, Fig. 3*B*, from the endocardium, respectively). However, regional differences in APD were attenuated due to the intercellular coupling. We also tested conditions with no transmural gradient in which all of the layers were composed of epicardial cells (Fig. 3*C*). Transmural dispersion of APD, APD

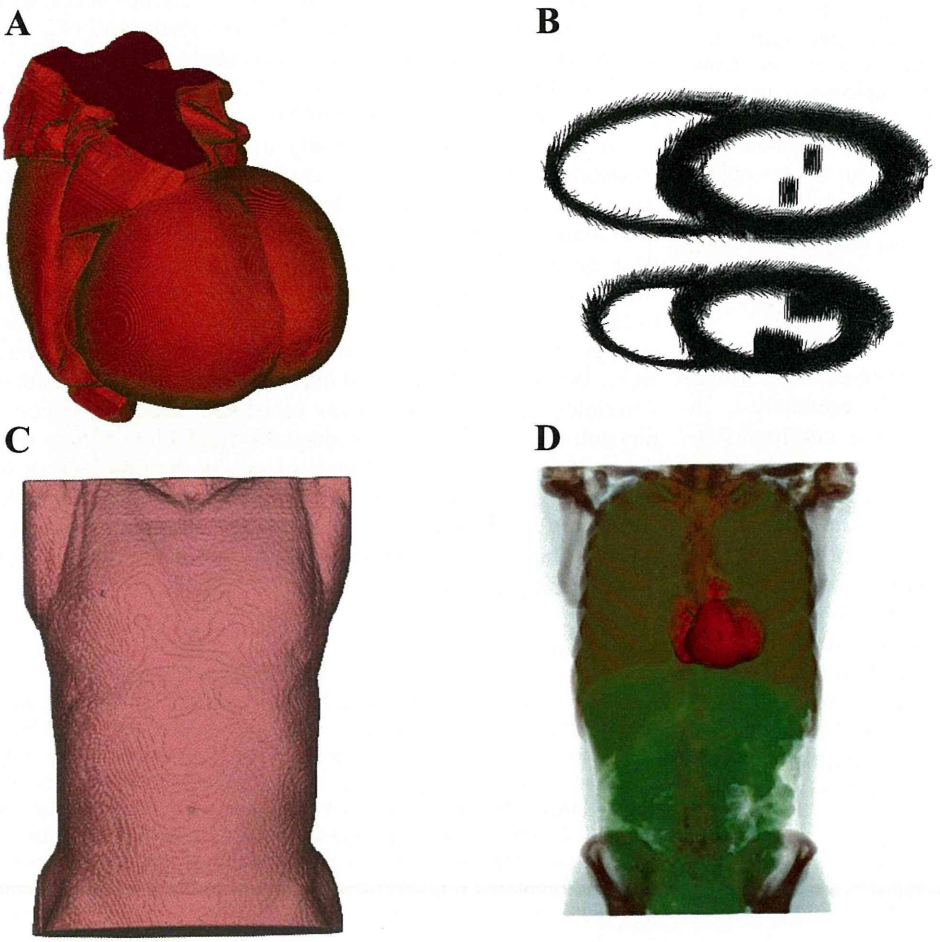

Fig. 1. Heart and torso models. *A*: human heart model with fine mesh. *B*: fiber directions mapped in the ventricles. *C*: torso model. *D*: transparent view showing the organs in the torso model.

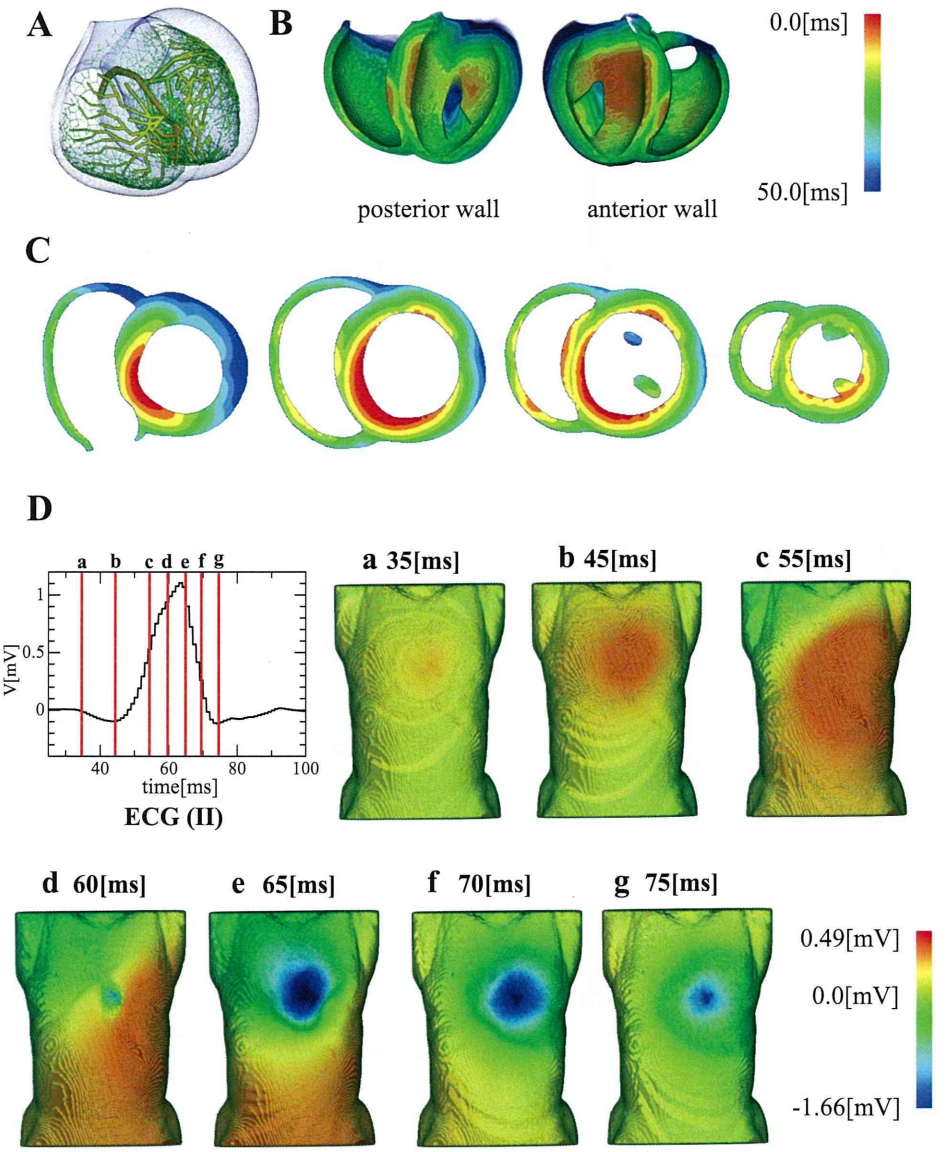

Fig. 2. Conduction system and ventricular activation. *A*: the conduction system with Purkinje fiber network. *B*: cut-out view of the ventricles showing activation sequence in color. *C*: isochronal map of activation in the transverse sections. *D*: sequential maps of the body surface potential during the activation phase. The timing of each map is indicated in the *top left* panel. V, voltage.

gradient, and the conduction velocity in these models are shown and compared with the experimental data (note that the *x*-axes are reversed for canine experimental data in Fig. 3, *D–F*). In Fig. 3*D*, APD distributions are shown for three models. The APD gradient of the model with M cells on the endocardial side (red line) showed general agreement with the canine heart (24), although the experimentally reported epicardial steep APD gradient was not observed in the simulation (Fig. 3*E*). Similarly, the simulation results did not show the epicardial gap in conduction velocity. Poelzing et al. (24) suggested that the epicardial APD gradient and the gap in conduction velocity are due to the heterogeneous expression of connexin 43 (Cx43), which we did not take into considerations in this study. However, the APD distribution reported for the human ventricular wall (12) did not show this epicardial gradient, thus closely resembling our simulation results.

As for the apicobasal gradient, Szentadrassy et al. reported a significant difference in the expression level of proteins forming the I_{Ks} channel between the apical and basal myocardium (38). We observed a similar trend for the transient outward K^+ current channel, although the difference in Kv4.3 was not significant. We modeled the apicobasal difference by regionally changing the I_{Ks} density. However, as detailed information on the distribution was not available, we introduced the linear apicobasal gradient with either 20 or 40% of the basal-to-apical ratio; these values were estimated from reported protein levels of these channels (38). We simulated the ECG for the nine combinations of these transmural and apicobasal APD gradients.

Computation. We used the IBM Blade Center consisting of 336 Power6 (4.0 GHz) processors for computation. The total number of degree of freedom was three hundred million, which took 6 h to calculate a single cardiac cycle.

RESULTS

Ventricular activation. Isochronal maps of ventricular activation are shown in Fig. 2, *B* and *C*, for the condition of endocardial M cells with no apicobasal gradient. As the conduction system was identical, we observed similar isochronal maps in all of the conditions tested; these data were similar to those previously reported (9). The temporal changes in body surface potential during the corresponding phase of ventricular activation (Fig. 2*D*; see also Supplemental Movie S1) were also in good agreement with published studies (6). Further-

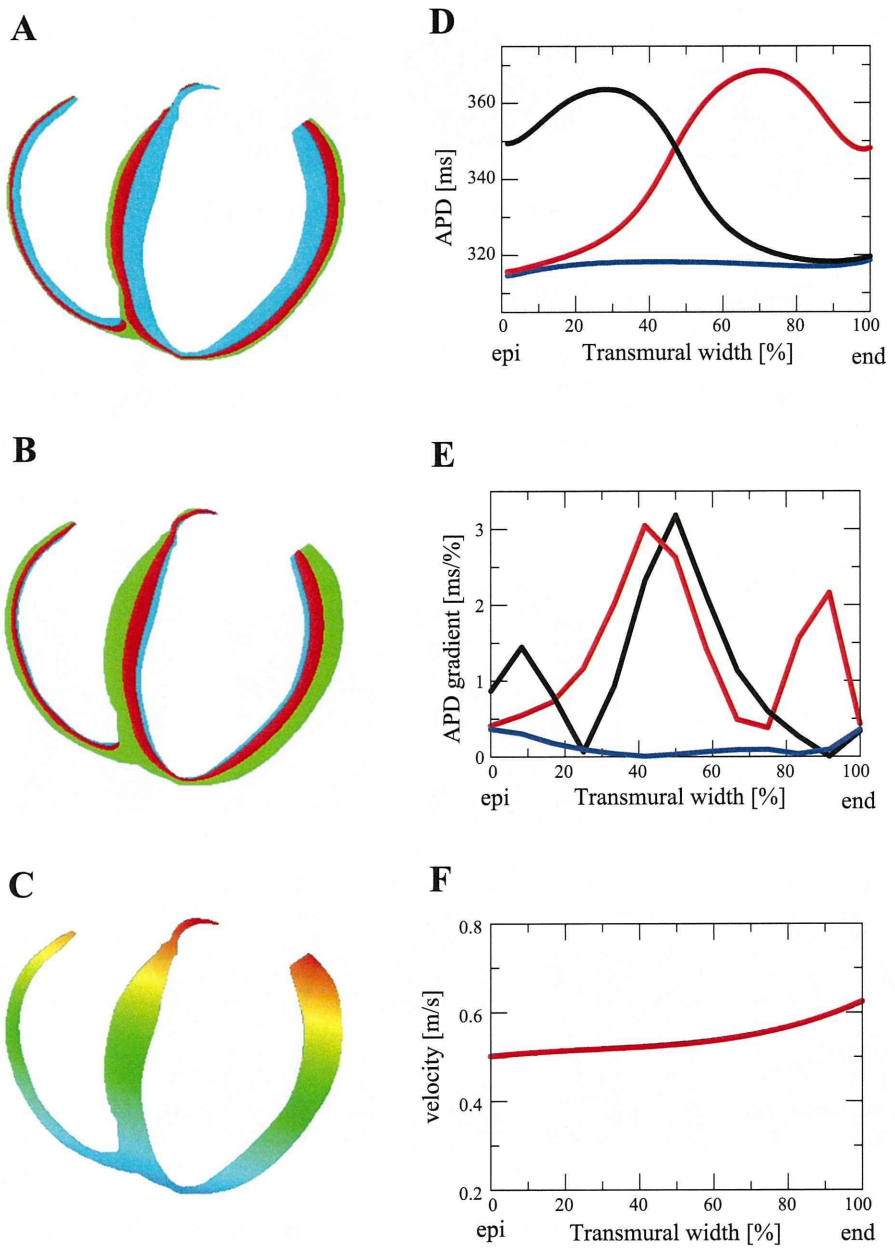

Fig. 3. Transmural distributions of M cell, action potential duration (APD), and conduction velocity. *A*: M cell located on the endocardial side. *B*: M cell located on the epicardial side. In *A* and *B*, the endocardial cell layer is indicated in blue, M cells in red, and epicardial cells in green. *C*: apicobasal APD gradients are shown in color from red (long) to blue (short). *D*: transmural ADP dispersion for the model shown in *A* (red line), *B* (black line), and *C* (blue line). *E*: APD gradient for the three models. Line colors are as in *D*. *F*: transmural distribution of conduction velocity.

more, the QRS complex of surface ECG generated from these body surface maps exhibited a similar standard morphology in all conditions (Fig. 4). Overall, these data indicate the validity of our modeling of the conduction system and also confirms that APD has little effect on the activation sequence in the ventricles.

APD dispersion and T wave. APD dispersion had a significant effect on the morphology of T waves (Fig. 4). In the normal cardiogram, the T waves were typically upright in I, II, and the lateral precordial leads (17), but were all negative in these leads in hearts with M cells on the epicardial side (Fig. 4, *G–I*). Nevertheless, even without the M cells, T waves become upright with a large apicobasal gradient (Fig. 4*C*). These data suggest that both the transmural (endo- to epicardial) and apicobasal gradients can generate upright T waves in these leads. Indeed, we obtained ECG with upright T waves in the following four conditions: *condition C*, no M cell with 40% apicobasal gradient; *condition D*, endocardial M cell with no apicobasal gradient; *condition E*, endocardial M cell with 20% apicobasal gradient; and *condition F*, endocardial M cell with 40% apicobasal gradient.

Nevertheless, there were significant differences in the T-wave characteristics between the conditions. In *condition C*, maximum amplitudes of T wave were small in both limbs, with the precordial leads measuring only 0.1 mV in V6. The T waves in the other conditions had a similar peak amplitude, but differed in morphology, particularly in their symmetry. For quantitative comparison, we calculated the asymmetry ratio defined as the ratio of the two areas (beginning-to-peak and peak-to-end) under the T curves of precordial leads for these conditions (Table 1). Asymmetry ratios in *condition C* were all less than unity, confirming the inverse asymmetry of the T waves in this condition. Interestingly, there was an inverse asymmetry (symmetry ratio < 1) in V6 for conditions with endocardial M cells, but without a large apicobasal gradient