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Letter to the Editor

Coexistence of two distinct fascinating cardiovascular disorders: Heterotaxy syndrome with left ventricular non-compaction and vasospastic angina

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A 31-year-old female was admitted to our hospital with an episode of severe prolonged chest tightness at rest. She was previously diagnosed with sick sinus syndrome (SSS) at 8 years old and had been closely followed by repetitive Holter monitoring, although no treatment ensued due to the absence of relevant symptoms (Fig. 1A) [1]. Echocardiography and cardiac magnetic resonance imaging (MRI) on admission revealed left ventricular non-compaction (LVNC), indicated by a thickened left ventricular wall consisting of a thin compacted epicardial layer and a markedly thickened endocardial layer, with numerous prominent trabeculations (Fig. 1B, Movies 1 and 2) [2]. To clarify the presence of simultaneous comorbidities, we performed whole-body computed tomography with contrast. Surprisingly, it revealed an inferior vena cava (IVC) anomaly, which was the absence of an IVC accompanied by azygous connection to the superior vena cava (Fig. 1C), intestinal malrotation (Fig. 1D), and accessory spleens (Fig. 1E). The cardiac anomalies, including SSS and LVNC, and the laterality sequence anomalies including azygous continuation of the IVC, intestinal malrotation, and polysplenia, were all compatible with a diagnosis of heterotaxy syndrome, left isomerism [3,4]. To elucidate the reason for her prolonged chest pain, we performed coronary angiography. Despite the coronary angiogram revealing no significant coronary stenosis, intracoronary administration of acetylcholine induced significant stenosis in the proximal to distal segment of the left anterior descending artery concomitant with typical chest oppression and ischemic ST segment changes in the electrocardiogram, which satisfied the positive diagnostic criteria for vasospastic angina (Fig. 2A–D) [5]. An association between coronary vascular dysfunction and atherosclerosis was unlikely in this case because she had neither risk factors for atherosclerosis nor other atherosclerotic diseases. Daily intake of a calcium channel blocker to inhibit the pathological coronary vasoconstriction totally relieved her chest symptom.

Heterotaxy syndrome is characterized by a wide variety of cardiac and extracardiac malformations that are primarily induced by disorders of left–right axis determination during early embryonic development [4]. LVNC is one of the cardiac malformations observed in heterotaxy syndrome, left isomerism [3], and chest pain is not uncommon in patients with LVNC. A previous study found that almost half of a patient group with LVNC presented with anginal chest pain, although most of these had a normal coronary angiogram [6] and the angina in LVNC might be due to relative chronic myocardial ischemia related to decreased coronary flow reserve and impaired microvascular function [7]. However, the detailed pathogenesis of these manifestations have not been fully elucidated, and the present case is the first to show clear evidence of chest pain in LVNC being due to intense vasoconstriction in the epicardial coronary artery. In addition, although LVNC and vasospastic angina are well-known fatal cardiovascular diseases, the majority of LVNC including heterotaxy syndrome cases and vasospastic angina cases are idiopathic and their genetic basis remains unclarified [3–5]. A recent study suggested that malfunctioning of a Rho-associated kinase could be related to the onset of heterotaxy syndrome [8], and this protein has also

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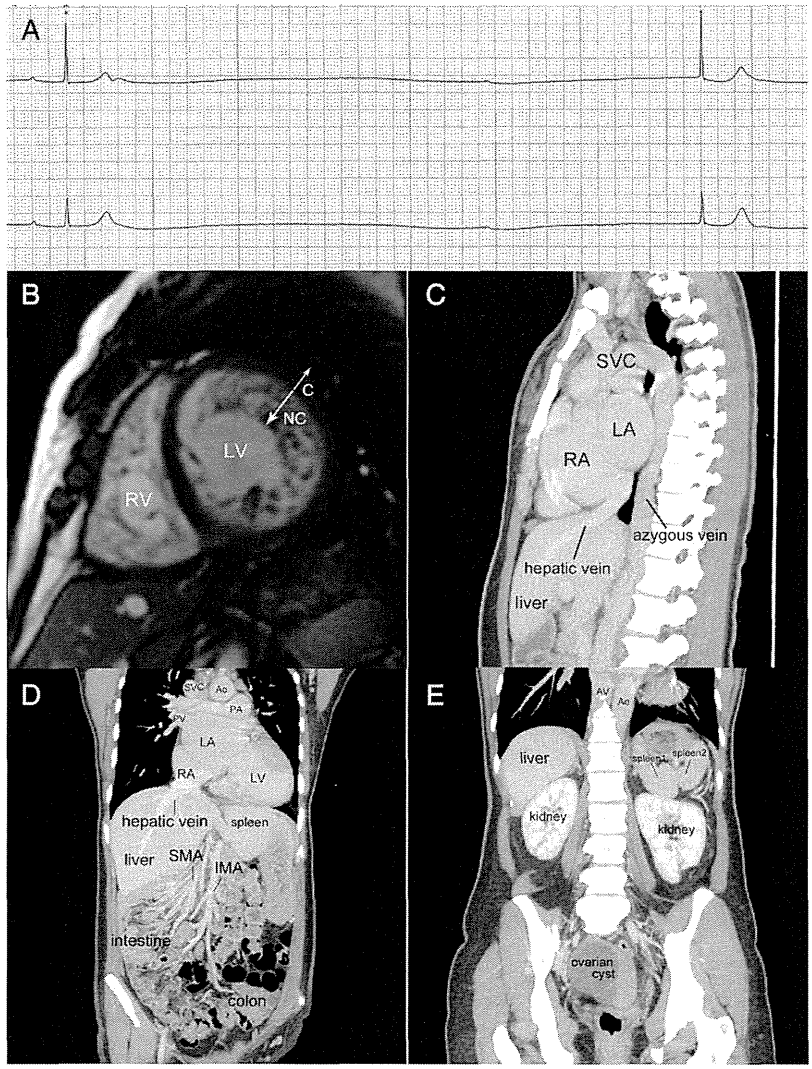

Fig. 1. Characteristics of heterotaxy syndrome, left isomerism. A) A representative trace demonstrating sick sinus syndrome by the Holter monitoring showed the maximum long pause of 7.4 s, which was the duration from sinus arrest to subsequent junctional escape beat, that was recorded during sleep, although the patient showed no relevant symptoms of this finding. Standard calibration and paper speed in both records was 10 small boxes/mv and 25 small boxes/s, respectively. B) Left ventricular (LV) end-diastolic apical short-axis view by cardiac magnetic resonance imaging showed a coarse and hypertrabeculated non-compacted left ventricle with a 2.8 NC/C ratio (double arrows). NC: non-compacted layer, C: compacted layer. C) Sagittal view by computed tomography (CT) showing the dilated azygous vein mimicking the aortic arch draining into the right superior vena cava (SVC). The hepatic vein directly returned into the right atrium. RA: right atrium, LA: left atrium. D) Coronal view by CT showing the intestinal malrotation by which the small bowel loops became located on the right side of the abdomen, and the colon became positioned on the left side. Ao: aorta, PA: pulmonary artery, PV: pulmonary vein, SMA: superior mesenteric artery, IMA: inferior mesenteric artery. E) Coronal view showing the accessory spleens. AV: azygous vein.

been implicated in causing vasospastic angina [5]. A further question whether both two diseases have shared molecular mechanisms for unmasking the disease phenotypes can be an interesting issue in the future.

This is the first report of a patient with heterotaxy syndrome with LVNC complicated by vasospastic angina, and this rare but intriguing finding highlights the possibility of further understanding the disease mechanism in heterotaxy syndrome with LVNC and vasospastic angina.

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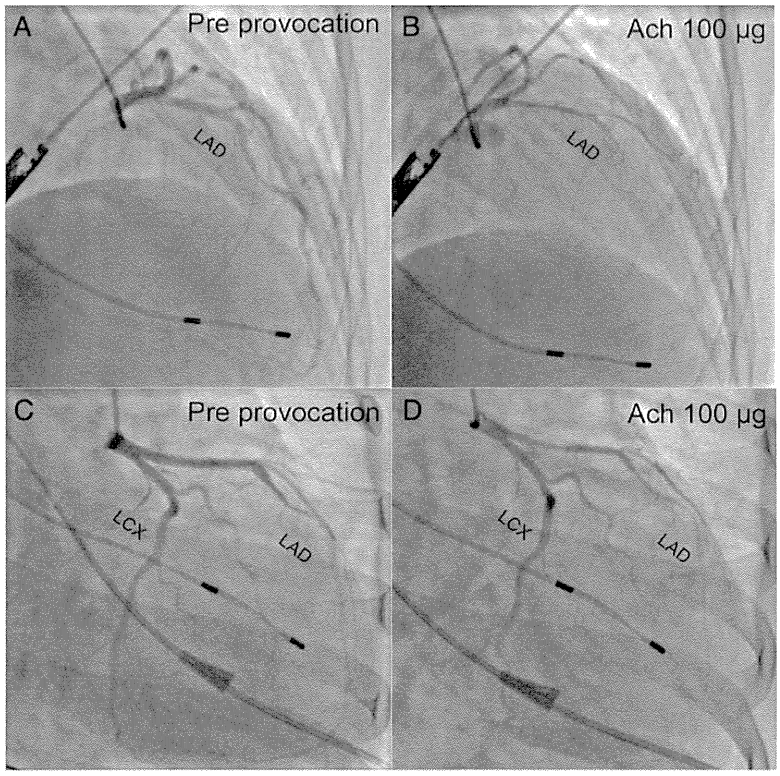

Fig. 2. Coronary angiography of left coronary artery before and after the acetylcholine provocation test. The right anterior oblique (RAO) cranial (A) and caudal (C) views by coronary angiogram before the provocation test showed normal coronary flow filling the distal coronary bed completely in the left anterior descending artery (LAD). The RAO cranial (B) and caudal (D) views by coronary angiogram after the provocation test with 100 μg acetylcholine showed obviously spastic LAD from the proximal to distal site, which was almost completely coronary occluded. LCX: left circumflex artery, Ach: acetylcholine.

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EDITORIAL

Current Status and Future Direction of Cardiac Resynchronization Therapy for Congenital Heart Disease and Pediatric Patients

Hitoshi Horigome, MD, PhD

Device therapy, including implantable cardioverter-defibrillator, cardiac resynchronization therapy (CRT), and CRT-D (CRT with a defibrillator), is currently considered an effective alternative for drug-resistant heart failure (HF) and prevention of sudden cardiac death (SCD). Several multicenter clinical trials have demonstrated that these therapies can improve left ventricular (LV) function and NYHA functional class and reduce all-cause mortality rate from HF and SCD.[1,2] Following its inclusion in the Governmental Health Insurance System, the use of device therapy for HF has increased exponentially in Japan. However, data on use of device therapy in congenital heart disease (CHD) and pediatric patients are scarce. In this issue of the Journal, Suzuki et al report for the first time the number of such cases and application of each type of device.[3] Considering the rapidly growing number of adult patients with CHD and improvement in the life expectancy of these patients, the report includes important information on the current status and issues to overcome for wider use of the technology. The article focuses on the application of CRT in CHD and the pediatric field.

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Prevalence of CRT Use

The nationwide questionnaire survey[3] provided several important data regarding current trends in CRT use in pediatric patients (<16 years of age). First, the number of children on CRT increased to 8–16 cases/year in 2008–2012. Also, DDD pacemakers, instead of CRT-P (CRT with a biventricular pacemaker) or CRT-D, were used for CRT in approximately two-thirds of patients younger than 5 years, despite interventricular delay being unable to be set in the former device. The wide use of DDD is probably because of the prohibition imposed by the Government on the use of the CRT-P in most children's hospitals that do not meet the institutional criteria. One advantage of CRT with a DDD pacemaker is its small size for children, although a Y-connector, which takes additional subcutaneous space, should be used for simultaneous biventricular pacing (Figure A).

Underlying Cardiac Diseases

Second, the underlying cardiac diseases are largely different from those in adults, in whom dilated cardiomyopathy (DCM) and ischemic heart disease are the main indications. A review of studies with enough number of pediatric patients[4–7] showed that the majority of patients had CHD, followed by cardiomyopathy and congenital heart block (CHB), and only a small number had left bundle branch block (LBBB) and other conduction disorders, in contrast to adults (Table).

As also shown in the Table, patients eligible for CRT can be divided into 3 groups: (1) systemic LV failure, (2) systemic right ventricular (RV) failure, and (3) HF with a single-ventricular physiology. Group 1 includes HF after corrective surgery for CHD, such as tetralogy of Fallot with right bundle branch block (RBBB), and that associated with RV single-site pacing for congenital or surgical atrioventricular block (AVB). The latter has gathered much interest since Tantengco et al[8] reported its adverse effects on LV function. Group 2 includes HF developing with aging rather than complex CHD (eg, corrected transposition of the great arteries, complete transposition of the great arteries corrected by atrial switch operation). Group 3 is unique to the pediatric field (ie, HF most typically develops after Fontan type surgery for single ventricle or hypoplastic right/left heart syndrome). It is remarkable that CRT can correct HF even in patients with such complex CHD.[9]

Patient Selection and Prediction of Responders

Even in adults with DCM, establishment of CRT eligibility criteria is still challenging but often includes NYHA functional class III or IV, ejection fraction <35%, and QRS duration >120 ms under optimal pharmacotherapy. Unfortunately, not all those who meet these criteria respond well to CRT and the non-response rate is up to 30%. The selection of pediatric patients for CRT is more difficult because of differences in the type of cardiac anomaly, ventricular morphology, conduction system and postoperative status. However, the lower rate of non-responders to CRT (12–16%) relative to adult patients is encouraging (Table). In the nationwide survey reported here,[3] the overall response rate was 83%, including those with single-ventricular physiology, similar to previous studies.[4–7]

In pediatrics, CRT for CHD typically started as an upgraded pacemaker in patients with a preexisting conventional pacemaker. Tantengco et al showed that long-term RV apical pacing from a young age can induce LV dysfunction,[8] which attracted a lot of interest because many pediatric cardiologists were aware of the phenomenon in patients with CHB. The au-

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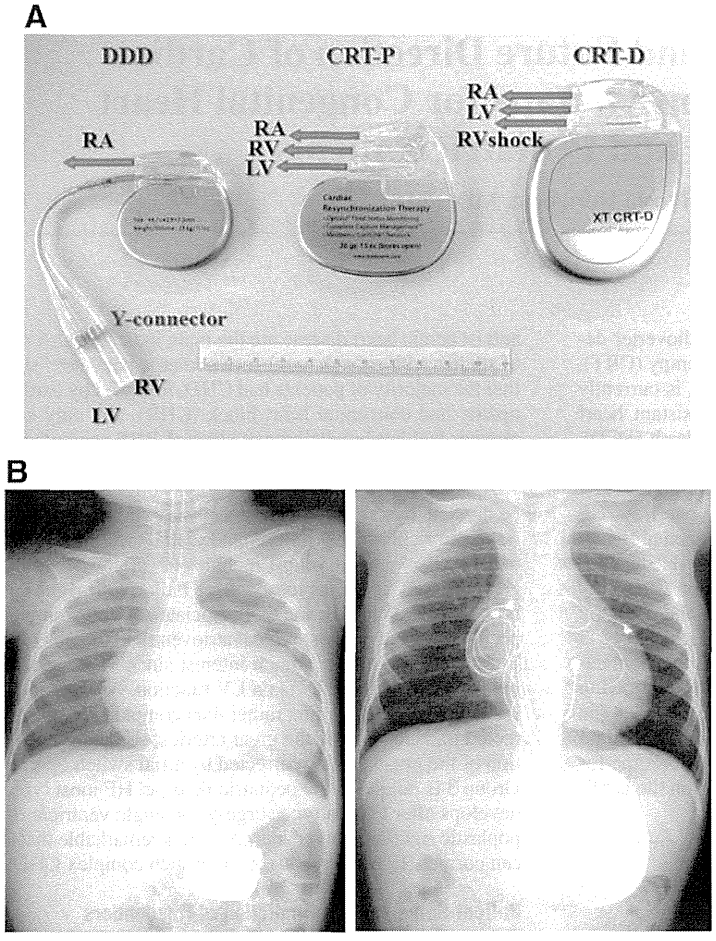

Figure. (A) Examples of conventional DDD, CRT with a biventricular pacemaker (CRT-P), and CRT with a defibrillator (CRT-D) for size comparison. The DDD device (**Left**) is smaller than the others but a Y-connector is necessary for simultaneous biventricular pacing, which occupies considerable subcutaneous space. Interventricular delay cannot be set in the DDD device, compared with the CRT-P (**Middle**) and CRT-D devices (**Right**), although the last one is much larger than the others. (B) Chest X-ray films of a 16-month-old patient, weighing 6.7 kg, with autoantibody-associated congenital complete heart block. Severe heart failure developed 11 months after implantation of right ventricular single-site pacemaker (**Left**). The child was transferred to Tsukuba University Hospital with intratracheal intubation, because the hospital admitting the patient did not meet the institutional criteria for CRT-P use. Heart failure resolved completely 8 months after pacemaker upgrade to CRT-P (**Right**). Cardiothoracic ratio decreased from 70 to 55%, and QRS duration shortened from 150 to 120 ms. Serum BNP fell from 6,520 before CRT to 28 pg/ml after CRT.

thors suggested biventricular pacing from early stage to prevent late-onset HF. In fact, Moak et al demonstrated that patients who developed DCM after conventional pacing for CHB showed reverse ventricular remodeling as well as clinical improvement following upgrading to atriobiventricular pacing.[10] **Figure B** shows a 1-year-old patient with autoantibody-related CHB who had major improvement following upgrading to CRT-P.

Echocardiography is frequently used to detect mechanical dyssynchrony, and many parameters have been proposed for that purpose in children with CHD.[11] However, a multicenter prospective study conducted recently in Japan (the J-CRT study)[12] did not find a single echocardiographic criterion that could significantly predict the response to CRT; rather, the response to therapy correlated with a combination of parameters of dyssynchrony between the septum and LV free wall measured by M-mode and tissue Doppler imaging, as well as LBBB on ECG. These results could not necessarily be applied to the field of CHD where RBBB instead of LBBB is a common cause of wide QRS and various ventricular morphologies are included. Thus, the indications for CRT should be assessed in individual patients with CHD. Recently, Seo et al demonstrated the usefulness of 3-dimensional speckle-tracking echocardiography in determining intraventricular regional mechanical activation, based on comparison with electrical voltage mapping.[13] This new imaging method seems promising and should be tried in CHD patients with various ventricular morphologies, including single ventricles.

Implantation Issues

Consideration of CRT use in pediatric or CHD patients is limited by various factors. Small body size is an obstacle for implantation of the generator, especially with CRT-D (**Figure A**). Transvenous lead implantation is precluded by complex venous anatomies, venous obstruction because of previous surgeries, and intracardiac shunt with right-to-left shunt. In the present nationwide survey,[3] approximately 90% of Japanese patients underwent CRT-P or CRT with a DDD pacemaker using epicardial leads. Lead dislodgement or fracture may also occur as the patient grows. Furthermore, inappropriate shock is a problem when a CRT-D is implanted in children.

Conclusions

CRT is a promising tool for CHD and pediatric patients with pharmacotherapy-resistant HF, with a lower failure rate com-

Table. Retrospective Studies of CRT in CHD and Pediatric Patients

	Dubin et al[4] (2005)	Khairy et al[5] (2006)	Cecchin et al[6] (2009)	Janousek et al[7] (2009)
n	103	13	60	109
Age, years, median (range)	12.8 (0.25–55.4)	6.5 (0.8–15.5)	15.0 (0.42–47)	16.9 (0.24–73.8)
Cardiac diagnosis				
CHD, n (%)	73 (71)	10 (77)	46 (77)	87 (80)
Systemic LV	49	6	26	47
Systemic RV	17	4	7	36
Single-ventricle	7	0	13	4
Cardiomyopathy, n (%)	16 (16)	3 (23)	10 (17)	10 (9)
CHB, n (%)	14 (13)	1 (7)	4 (7)	12 (11)
Conduction disorders, n (%)				
AVB	ND	10 (77)	41 (68)	84 (77)
LBBB	ND	ND	10 (17)	10 (9)
RBBB	ND	ND	4 (7)	5 (5)
Non-specific IVCD	ND	3 (23)	5 (8)	10 (9)
QRS duration (ms)				
Pre-CRT	166±33	ND	Mean 149	Median 160
Post-CRT	126±24	ND	Mean 120	Median 130
Systemic ventricular EF (%)				
Pre-CRT	26.2±11.6	31.4±13.5	Median 35, 8–57	Median 27
Post-CRT	39.9±14.8	50.6±15.2	Median 44, 13–73	Median 38.5
NYHA				
Pre-CRT	Class III or IV in 39 (38%)	ND	Class II (42%), III (25%), IV (7%)	Median Class 2.5
Post-CRT	ND	ND	Improved in 39/45 (87%)	Median Class 1.5
Non-responders, n (%)	11/89 (12)	ND	6/45 (13)	15/94 (16)

AVB, atrioventricular block; CHB, congenital heart block; CHD, congenital heart disease; CRT, cardiac resynchronization therapy; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LV, left ventricle; ND, not described; RBBB, right bundle branch block; RV, right ventricle.

pared with adult patients. However, there are currently no guidelines for selection of patients and devices and these are not easy to establish because of the heterogeneity of the disease. Also, the majority of children's hospitals in Japan are currently not allowed to use CRT-P or CRT-D devices because they do not meet the institutional criteria for such use.[14] Revision of the criteria to allow wider use of these devices in children's hospitals should further reduce the mortality of CHD and pediatric patients.

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EDITORIAL

E1784K Mutation in *SCN5A* and Overlap Syndrome

Naokata Sumitomo, MD, PhD

Congenital long QT syndrome (LQTS) is characterized by prolongation of the QT interval on the surface ECG and may cause syncope and seizures; there is a certain risk of fatal ventricular arrhythmias, torsade de pointes or ventricular fibrillation.[1] The QT interval is determined by the cardiac action potential duration and is related to the many ion channels in the myocardial cells. The most important state of the ion currents for prolonging the QT interval is a decrease in the outward K current, and increase of the inward Na or Ca current. *SCN5A* is the gene encoding the most prevalent cardiac Na channel α subunit, and an *SCN5A* mutation is responsible for many hereditary arrhythmias including type 3 LQTS (LQT3),[2] Brugada syndrome (BrS),[3] progressive cardiac conduction disturbances (PCCD),[4] sick sinus syndrome (SSS),[5,6] atrial fibrillation,[6,7] atrial standstill, and sudden infant death syndrome (SIDS).[8–10]

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The most common *SCN5A* mutation in LQT3 causes a persistent Na current during the action potential plateau because of malfunctioning of the fast Na channel inactivation,[2] and this delayed inactivation delays the repolarization of the myocardial cells, and leads to prolongation of the QT interval (Table).

In contrast, a reduction in the initial opening of the Na channels in the right ventricular epicardial cells may cause ST elevation in the right precordial leads and lead to BrS (Table).

Some PCCD patients develop this phenotype with aging, because the increased chance of fibrosis in association with genetic defects may impair propagation of the impulse through the conduction system. In some PCCD patients, a conduction defect is documented from birth. Depending on the consequence of the mutation on the sodium channels, the phenotype may be progressive or congenital (Table).[4]

If the action potential generation and/or propagation is more severely impaired in the atria than in the ventricles in *SCN5A* mutation patients, the sinus node dysfunction caused by failure of the impulses to conduct into the adjacent atrial myocardium (exit block) has been suggested as a cause of SSS, atrial standstill, and atrial fibrillation (Table).[5]

Mutations of E1784K in *SCN5A* cause a persistent (late) inward Na^+ current, and also cause a reduction in the peak Na^+ current.[9,11,12] Some LQT3 patients present with ECG findings characteristic of BrS (overlap syndrome), and one of the causes of this overlapping syndrome can be explained by E1784K,[11,12] 1795insD,[13,14] ΔKPQ,[12,15] and ΔK1500.[16] However, several other biophysical mechanisms may be related to the reduction in the peak Na current.[17]

Sodium-channel blockers are commonly used in patients with LQT3 because of the blocking effect on persistent Na currents.[18–20] However, in overlap syndrome, sodium-channel blockers shorten the QT interval, possibly reducing the peak Na current, and thus uncover a concealed BrS resulting in typical ST segment elevation in the right precordial leads, and may provoke malignant ventricular arrhythmias.[14]

In this issue of the Journal, Takahashi et al report that the E1784K mutation in *SCN5A* is the most prevalent mutation in school children with LQTS in the Okinawa islands.[21] The most common mutation in LQTS is reported to be a *KCNQ1* mutation.[22,23] It is noteworthy that there is a high prevalence rate of

Table. *SCN5A* Mutations and Associated Inherited Arrhythmias

Syndrome	Phenotype	Possible cause of the syndrome
LQT3	Prolonged QT	Persistent Na current
BrS	RBBB type QRS, ST elevation in the right precordial leads	Reduction in the initial opening of the Na channels in the epicardial right ventricular outflow tract cells
PCCD	BBB, AVB	Fibrosis and conduction disturbance of the conduction system
SSS	Sinus bradycardia, SA block	Failure of conduction from the sinus node (exit block), morphological changes in the atrial cells
Atrial standstill	Junctional rhythm without P waves	Failure of conduction in the atrium
AF	AF	Morphological changes of the atrial cells
Overlap syndrome	LQT3, BrS, SSS	Persistent Na current and reduction in the initial Na current

AF, atrial fibrillation; AVB, AV block; BBB, bundle branch block; BrS, Brugada syndrome; LQT3, long QT type 3; PCCD, progressive cardiac conduction system disturbance; RBBB, right bundle branch block; SA block, sino-atrial block; SSS, sick sinus syndrome.

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LQT3 (63%) in the Okinawa islands, and all the mutations are E1784K in *SCN5A*.[21] From this result, the ancestors of the Okinawa islands may differ from those of the other islands in Japan. As reported, BrS is much more prevalent in the Asian region,[24] and we need to investigate the prevalence of LQT3 incidence and also E1784K mutations in *SCN5A*.

In the study by Takahashi et al,[21] one in 8 of the phenotypes was revealed to have the BrS-type ST elevation while taking mexiletine. Those patients may have an overlapping syndrome of LQT3 and BrS. A closer look at the ST changes in the right precordial leads and 3rd intercostal space right precordial lead recording may be needed when an LQT3 gene anomaly is found, especially an E1784K mutation in *SCN5A*. Further, great care also must be taken when using sodium-channel blockers and β-blockers in patients with LQT3.

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Original Article

Early Repolarization Increases the Occurrence of Sustained Ventricular Tachyarrhythmias and Sudden Death in the Chronic Phase of an Acute Myocardial Infarction

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Background—We recently showed that the presence of early repolarization (ER) increases the risk of ventricular fibrillation occurrences in the early phase of acute myocardial infarction (AMI). This study aimed to clarify whether an association exists between ER and occurrences of ventricular tachyarrhythmias or sudden death in the chronic phase of AMI.

Methods and Results—This study retrospectively enrolled 1131 patients (67±12 years; 862 men) with AMIs surviving 14 days post-AMI. The primary end point was the occurrence of sustained ventricular tachyarrhythmias or sudden death >14 days after the AMI onset. We evaluated the presence of ER from the predischarge ECG (mean 10±3 days post-AMI). ER was defined as an elevation of the terminal portion of the QRS complex of >0.1 mV in inferior or lateral leads. After a median follow-up of 26.2 months, 26 patients had an episode of ventricular tachyarrhythmias or sudden death. A multivariable Cox regression analysis revealed the presence of ER (hazard ratio, 5.37; 95% confidence interval, 2.27–12.69; $P<0.001$), Killip class on admission of >I (hazard ratio, 2.75; 95% confidence interval, 1.24–6.07; $P=0.013$), and a left ventricular ejection fraction of <35% (hazard ratio, 11.83; 95% confidence interval, 5.16–27.13; $P<0.001$) were significantly associated with event occurrences. As features of the ER pattern, ER in the inferior leads, high-amplitude ER, a notched morphology, and ER without ST-segment elevation were associated with an increased risk of event occurrences.

Conclusions—ER observed at a mean of 10 days post-AMI may be a marker for a subsequent risk of ventricular tachyarrhythmias or sudden death. ***(Circ Arrhythm Electrophysiol.* 2014;7:626-632.)**

Key Words: acute myocardial infarction ■ arrhythmia ■ death, sudden, cardiac ■ early repolarization

Early repolarization (ER) has historically been regarded as an innocuous finding in healthy young people.[1,2] Although considered benign, the potential role of ER in arrhythmogenicity has been suggested in experimental studies.[3] Recently, several case reports have called our attention to the association of idiopathic ventricular fibrillation (VF) with J-point elevation.[4–8] In addition, recent evidence has linked ER to idiopathic VF in patients with no structural heart disease[9–13] and to life-threatening ventricular tachyarrhythmias (VT/VF) associated with chronic coronary artery disease.[14]

Clinical Perspective on p 632

We recently showed that the presence of ER increases the risk of VF occurrences in the early phase of an acute myocardial infarction (AMI).[15] However, it is unknown whether there is an association between ER and VF occurrences in the chronic phase of an AMI. Accordingly, the purpose of this study was to clarify this point.

Methods

Study Population

Between April 2006 and February 2012, 1306 consecutive Japanese patients with an AMI who underwent percutaneous coronary intervention at the University of Tsukuba Hospital, Tsukuba Medical Center Hospital, and Ibaraki Prefectural Central Hospital were included in the present retrospective study. Patients were eligible if they were ≥18 years and presented within 24 hours of the onset of symptoms associated with an AMI. Sixty-five patients died within 14 days after the AMI onset. All 8 patients who experienced sustained VT/VF between 2 and 14 days after the AMI onset died within 14 days after the AMI onset. Sixty patients had experienced a prior AMI, 3 had a Brugada ECG pattern,[16] and 47 were lost to follow-up. After excluding these patients, the remaining 1131 patients (862 men and 269 women; mean age, 67±12 years) were finally included in this study (Figure 1). We included patients with a prolonged QRS complex duration of >120 ms, which is well known as a risk marker for cardiac events[17]; however, it is not possible to measure the ER in such cases.

The primary end point of this study was the occurrence of sustained VT/VF or sudden death >14 days after the onset of the AMI. Patients were classified on the basis of the occurrence of sustained

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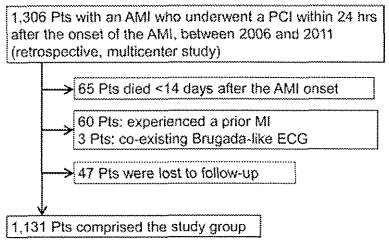

Figure 1. Study design. Patients who were excluded from the analysis are indicated by arrows directed to the right. AMI indicates acute myocardial infarction; PCI, percutaneous coronary intervention; and Pts, patients.

VT/VF or sudden death, and the clinical data were analyzed in both the event occurrence and no event occurrence study groups. Data collection covered the age, sex, cardiovascular risk factors, culprit artery, number of diseased coronary arteries, Killip class on admission, medications before discharge, VT/VF occurrence within 48 hours after the onset of the AMI, left ventricular ejection fraction, and infarct size (based on the peak creatine kinase rise). Hypertension, hypercholesterolemia, and diabetes mellitus were scored on the basis of the previous diagnosis and initiation of therapy. Ethical approval was obtained from the institutional review board of each participating hospital, and all patients gave their written informed consent before participation.

An AMI was defined as a rise in the MB fraction of the creatine kinase above the 99th percentile of the upper reference limit together with symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), and the development of pathological Q waves on the ECG.[18] An ST-elevation myocardial infarction was defined as an AMI with new ST elevation at the J point in 2 continuous leads with the following cutoff points: ≥0.2 mV in men or ≥0.15 mV in women in leads V_2 to V_3 and ≥0.1 mV in the other leads.[18] Successful percutaneous coronary intervention was defined as the attainment of a thrombolysis in myocardial infarction 3 flow. We defined sudden death as that occurring within 1 hour of the onset of symptoms. The definition of sustained VT/VF was that lasting longer than 30 seconds or that requiring adequate therapy with an implantable cardioverter defibrillator (ICD).

ECG Analysis

To blind the ECG interpreters from the clinical characteristics and patient groupings, all tracings were scanned and coded. We evaluated the 12-lead ECG recorded before the AMI onset (if possible), just after the onset of the AMI, and before discharge. In case the duration of the patient's hospitalization was >14 days, an ECG obtained around 14 days after the onset of the AMI was assessed. The mean duration from the onset of the AMI to the predischarge ECG recording was 10±3 days. ER was electrocardiographically defined as an elevation of the terminal portion of the QRS complex of >0.1 mV in ≥2 contiguous inferior (II, III, and aVF) or lateral (I, aVL, and V_4–V_6) leads, manifested as QRS notching or slurring (Figure 2). A notched ER was defined as an upward deflection and slurring as a conduction delay beginning on the QRS downstroke.[19,20] The amplitude of the ER was measured from the onset of the QRS slur in the case of slurred ER or the peak of the end of the QRS notch in the case of notched J waves[20] and relative to the QRS onset to minimize any baseline wandering effect.[14] We analyzed the inferior and lateral ER independently to clarify the significance of the localization and used 2 predefined cutoff points (≥0.1 mV and ≥0.2 mV) to assess the significance of the amplitude of the ER from baseline. The morphological characteristics of the ER (notching or slurring) were also analyzed independently.[19,20] The anterior precordial leads (V_1–V_3) were excluded from the analysis of the ER to avoid the inclusion of patients with right ventricular dysplasia or Brugada syndrome.[16,21] We also analyzed the ST-segment elevation independently to clarify the significance of the ST-segment characteristics according to the criteria proposed by Heng et al[20] and Uberoi et al[19]: ST-segment elevation was defined as an elevation of the ST junction of ≥0.1 mV and upward sloping of the ST segment. We assessed the prevalence, localization, amplitude, morphology, and ST segment of the ER in both patient groups. Two trained investigators independently evaluated the baseline 12-lead ECGs for the presence of ER with no knowledge of the other observer's judgment or the clinical information. A third observer was consulted in the case of disagreement. All ECGs containing an ER pattern were double-checked, and the grading was established by consensus. The interobserver variability was assessed in all patients. In 100 randomly selected patients, one observer evaluated a new arbitrary judgment on a separate occasion to determine the intraobserver variability.

Statistical Analysis

Continuous variables are expressed as the means±SD or medians (interquartile range [IQR]). Comparisons between 2 groups were tested by an unpaired *t* test or Mann–Whitney *U* test according to the data distribution with or without normality. All categorical variables are presented as the number and percent in each group and were compared by a χ^2 analysis or Fisher exact test. An overall χ^2 test for a 2×n table was constructed when comparisons involved >2 groups. A comparison of the probability of the freedom from the occurrence of VT/VF or sudden death between those with and without ER was

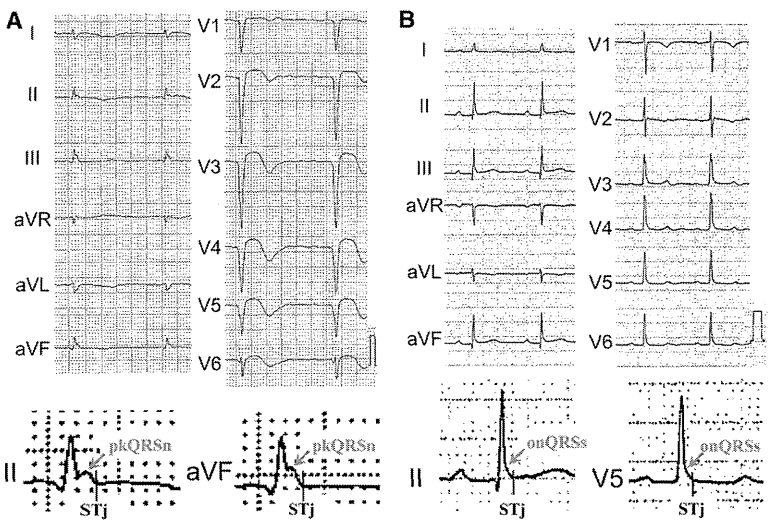

Figure 2. Representative cases of early repolarization. **A**, Notched early repolarization (arrows) without ST-segment elevation in the inferior leads was observed in an 80-year-old man after an anterior myocardial infarction. **B**, Slurred early repolarization (arrows) without ST-segment elevation in the inferior and lateral leads was recognized in a 77-year-old woman after an anterior myocardial infarction. The arrows point to the measurement point of the amplitude of the peak QRS notch and QRS slur; the hash lines at the end of the QRS indicate the ST junction where we assessed the ST-segment elevation. onQRSs indicates onset of the QRS slur; pkQRSn, peak QRS notch; and STj, ST junction.

performed using a Kaplan–Meier survival analysis with a log-rank test. Time 0 for the survival analyses was the date of the AMI onset. A univariable analysis of the patient characteristics was compared between the event occurrence group and no event occurrence group, and a forward stepwise multivariable Cox proportional regression analysis was performed to detect any independent significant predictors by adjusting for multiple variables (reported as the hazard ratio with a 95% confidence interval [CI]). Variables, including multivariable Cox proportional hazard models, were those that achieved statistical significance ($P<0.05$) or that were close to significance ($P<0.1$) in the univariable analysis. Significant and independent predictors for the occurrence of VT/VF or sudden death detected by the Cox proportional hazard regression model were assessed using the Harrell's c index. The intraobserver and interobserver variability was investigated by κ statistics. A P value of <0.05 was considered statistically significant. All analyses were performed with a PASW Version 17.0 statistics software package (SPSS, Chicago, IL).

Results

Demographic and Clinical Characteristics of All the AMI Patients

Among the 1131 patients, 26 (2.3%) experienced an episode of VT/VF or sudden death during a median follow-up period of 26.2 (IQR, 14.2–43.5) months. Nonresuscitated sudden death occurred in 16 patients, VF in 7, and ventricular tachycardia in the remaining 3. Among the 16 patients who experienced sudden death, VF was documented in 4 patients. There was no statistically significant difference in the age, cardiovascular risk factors, number of diseased coronary arteries, peak creatine kinase level, medications other than statins, or prevalence of ST-elevation myocardial infarction, a successful percutaneous coronary intervention, or prolonged QRS duration between the 2 groups. However, the prevalence of a male sex ($P=0.016$), left anterior descending culprit artery ($P=0.044$), VT/VF occurrence within 48 hours after the onset of the AMI ($P=0.007$), and an ICD implantation ($P=0.013$) were higher and that of statin administration was lower ($P=0.014$) in patients with event occurrences than in those without (Table 1). Furthermore, the patients with event occurrences had a lower ejection fraction ($P<0.001$), greater prevalence of an ejection fraction of <35% ($P<0.001$), and higher Killip class ($P=0.009$) than those without (Table 1).

ER was present in 99 of 1131 patients on the 12-lead ECG obtained before discharge and was more common in patients with event occurrences than in those without ($P=0.001$, Table 1). The prevalence of ER assessed before discharge did not differ between the patients with an ST-elevation myocardial infarction and those with a non–ST-elevation myocardial infarction (9% versus 8%; $P=0.76$). Kaplan–Meier curves showed that the presence of ER on the 12-lead ECG obtained before discharge was associated with an increased occurrence of VT/VF or sudden death ($P<0.001$ by log-rank test, Figure 3). The median duration from the AMI onset to the VT/VF or sudden death occurrence was 7.3 months (IQR, 2.3–35.6) in the 26 patients with an event occurrence and shorter in those with ER than in those without ER (1.7 months [IQR, 0.9–7.0] versus 14 months [IQR, 4.1–41.4]; $P=0.023$).

In the subgroup analysis of the patients with a left ventricular ejection fraction of <35%, concomitant ER was also associated with an increased risk of VT/VF or a sudden death occurrence ($P=0.021$ Figure 4A).

There were no significant differences in the baseline characteristics between those enrolled in our study and those who were eligible but were lost to follow-up.

Detailed Characteristics of ER for Predicting an Event Occurrence

Distribution

Among the 99 patients who had ER on the 12-lead ECG obtained before discharge, the J-point elevation was in the inferior leads in 68 (69%) patients, in the lateral leads in 23 (23%), and in the inferior and lateral leads in the remaining 8 (8%, Table 1). The patients with an event occurrence were more likely to have ER in the inferior leads than those without an event occurrence (27% versus 6%; $P=0.001$, Table 1), whereas the prevalence of ER in the lateral leads or both leads did not differ significantly between the 2 groups (Table 1).

Magnitude and Morphology

An amplitude of the ER of >0.2 mV was found in the inferior or lateral leads in 29 (3%) patients and was more prevalent in the patients with event occurrences than in those without (12% versus 2%; $P=0.027$, Table 1).

The prevalence of a notched ER differed significantly between the patients with and without event occurrences (23% versus 6%; $P=0.004$, Table 1). By contrast, the incidence of slurring did not differ significantly between the 2 groups ($P=0.1$, Table 1). Kaplan–Meier curves showed that the prevalence of the occurrence of VT/VF or sudden death significantly differed among the patients with a notched ER, slurred ER, and without ER ($P=0.001$ by log-rank test, Figure 4B).

ST Segment

The prevalence of ER without ST-segment elevation significantly differed between the patients with and without event occurrences (31% versus 6%; $P<0.001$, Table 1). Conversely, the incidence of ER with ST-segment elevation did not differ significantly between the 2 groups ($P=1.0$, Table 1).

Correlation Between the Location of the ER and the Territory of the Culprit Artery

The location of the ER matched with the territory of the culprit artery in 26 (2%) patients. There was no significant difference in the prevalence of matching between the ER and culprit artery between the patients with and without event occurrences (Table 1).

Predictors of VF Occurrences in the Chronic Phase of an AMI

A multivariable Cox proportional regression analysis revealed that a left ventricular ejection fraction of <35% (hazard ratio, 11.83; 95% CI, 5.16–27.13; $P<0.001$), the presence of ER on the 12-lead ECG obtained before discharge (hazard ratio, 5.37; 95% CI, 2.27–12.69; $P<0.001$), and a Killip class on admission of >I (hazard ratio, 2.75; 95% CI, 1.24–6.07; $P=0.013$) were independent predictors of the occurrence of VT/VF or sudden death during the follow-up period (Table 2). The Harrell's c index of the Cox proportional hazard regression model including the ejection fraction <35%, high Killip class, and presence of ER was

Table 1. Demographic and Clinical Characteristics of the Patients With and Without Occurrences of Ventricular Tachyarrhythmias or Sudden Death

	Total (n=1131)	Event Occurrence (n=26)	No Event Occurrence (n=1105)	*P* Value
Age, y	67±12	69±8	67±12	0.376
Male sex, n (%)	862 (76%)	25 (96%)	837 (76%)	0.016
Cardiovascular risk factors				
Hypertension, n (%)	710 (62%)	18 (68%)	692 (62%)	0.491
Hyperlipidemia, n (%)	516 (46%)	11 (42%)	505 (46%)	0.731
Diabetes mellitus, n (%)	388 (34%)	13 (50%)	375 (34%)	0.088
Smoking, n (%)	637 (56%)	15 (58%)	622 (56%)	0.887
Culprit artery*				
RCA, n (%)	394 (35%)	5 (19%)	389 (35%)	0.091
LAD, n (%)	519 (46%)	17 (65%)	502 (45%)	0.044
LCx, n (%)	198 (18%)	4 (15%)	194 (18%)	1.0
LMT, n (%)	36 (3%)	0 (0%)	36 (3%)	1.0
No. of diseased coronary arteries, n	1 [1–2]	1.5 [1.0–2.8]	1 [1–2]	0.448
Killip class on admission, n (%)				0.009
I	909 (80%)	15 (58%)	894 (81%)†	
II	108 (10%)	4 (15%)	104 (9%)	
III	48 (4%)	2 (8%)	46 (4%)	
IV	66 (6%)	5 (19%)	61 (6%)‡	
Medication				
Statin, n (%)	878 (78%)	15 (58%)	863 (78%)	0.014
β-Blocker, n (%)	766 (68%)	14 (54%)	752 (68%)	0.126
ACE-I/ARB, n (%)	831 (73%)	21 (81%)	810 (73%)	0.394
Calcium blocker, n (%)	228 (20%)	3 (12%)	225 (20%)	0.268
Acetylsalicylic acid, n (%)	1129 (100%)	26 (100%)	1103 (100%)	1.0
Clopidogrel, n (%)	1109 (98%)	26 (100%)	1083 (98%)	1.0
VT/VF occurrence in the acute phase, n (%)	78 (7%)	6 (23%)	72 (7%)	0.007
Peak creatine kinase levels, U/L	1625 [708–2926]	2370 [1278–3541]	1602 [701–2916]	0.101
Left ventricular ejection fraction, %	53±11	42±12	54±11	<0.001
Left ventricular ejection fraction <35%, n (%)	54 (5%)	9 (35%)	45 (4%)	<0.001
STEMI, n (%)	924 (82%)	20 (77%)	904 (82%)	0.606
Successful PCI, n (%)	1102 (97%)	25 (96%)	1077 (97%)	0.495
Implantable cardioverter defibrillator, n (%)	8 (1%)	2 (8%)	6 (1%)	0.013
ECG parameters obtained from the ECG before discharge				
QRS complex duration >120 ms, n (%)	46 (4%)	1 (4%)	45 (4%)	1.0
CRBBB, n (%)	36 (3%)	0 (0%)	36 (3%)	1.0
CLBBB, n (%)	10 (1%)	1 (4%)	9 (1%)	0.208
Early repolarization, n (%)	99 (9%)	8 (31%)	91 (8%)	0.001
Distribution				
Inferior leads, n (%)	68 (6%)	7 (27%)	61 (6%)	0.001
Lateral leads, n (%)	23 (2%)	0 (0%)	23 (2%)	1.000
Both leads, n (%)	8 (1%)	1 (4%)	7 (1%)	0.170
Matched to the territory of culprit artery, n (%)	26 (2%)	1 (4%)	25 (2%)	0.417
Amplitude of J point				
≥0.2 mV	29 (3%)	3 (12%)	26 (2%)	0.027
Morphology				
Notching	72 (6%)	6 (23%)	66 (6%)	0.004
Slurring	27 (2%)	2 (8%)	25 (2%)	0.126
ST segment				
ER with ST-segment elevation	28 (2%)	0 (0%)	28 (3%)	1.000
ER without ST-segment elevation	71 (6%)	8 (31%)	63 (6%)	<0.001

Values are reported as the mean±SD, median (interquartile range), or n (%). ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; ER, early repolarization; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; and VT/VF, ventricular tachyarrhythmia.

*There were no patients who had >1 culprit artery.

‡$P<0.05$ and †$P<0.01$ vs event occurrence.

0.693 (95% CI, 0.666–0.720; $P<0.001$) for the occurrence of VT/VF or sudden death.

Time Course of ER

Among the 99 patients with ER on the ECG obtained at predischarge, ER was also observed on the ECG recorded just after the onset of the AMI in only 37 (37%) patients. By contrast, in the remaining 62 (63%) patients, it could not be definitely confirmed on the ECG recorded just after the onset of the AMI because of the ST elevation or reciprocal ST depression caused by the AMI itself (Figure 5). ER assessed by the ECG recorded just after the onset of the AMI was not associated with an event occurrence ($P=0.3$ by the log-rank test).

Among the 234 patients in whom we could assess the ECG obtained before the onset of the AMI, the presence or absence of ER in the ECG obtained before the AMI onset and before discharge matched in the majority of the patients; 22 (67%) of 33 patients had ER in the ECG obtained both prior to the AMI onset and at predischarge, and 195 (97%) of 201 patients did not have ER in the ECG obtained neither prior to the AMI onset nor at predischarge. On the other hand, the ER disappeared in 11 (33%) of 33 patients who had ER in the ECG obtained before the AMI onset due to the ST-T change caused by the AMI itself. ER was acquired in 6 (3%) of 201 patients who did not have ER prior to the AMI onset (Figure 6).

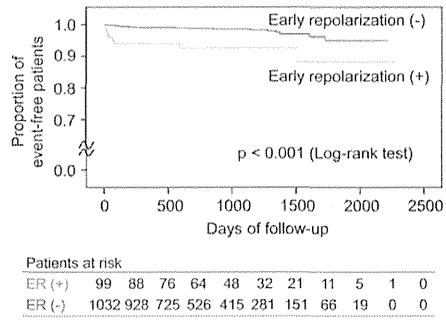

Figure 3. Kaplan–Meier curves. There was a significant difference in the occurrence of sustained ventricular tachyarrhythmias or sudden death between the patients with and without early repolarization (ER).

Reproducibility of the Judgment of ER

The intraobserver variability for ascertaining the presence of ER on the ECG was κ=0.90 (P<0.001), and the interobserver variability was κ=0.89 (P<0.001).

Discussion

Main Findings

To the best of our knowledge, the results of this study showed for the first time the following findings: (1) ≈10% of the AMI patients studied had ER on the ECG recorded at predischarge; (2) about one third of the patients who developed VT/VF or sudden death in the chronic phase of an AMI had ER; (3) not only severe left ventricular dysfunction and high Killip class on admission but also ER were independent predictors of the occurrence of VT/VF or sudden death; (4) as features of an ER pattern, ER in the inferior leads, high-amplitude ER, a notched morphology, and ER without ST-segment elevation were significantly associated with an event occurrence; and (5) the ER pattern was not well recognized in the ECG obtained shortly after the onset of the AMI in 64% of the patients who had ER at predischarge. In addition to a VF occurrence in the acute phase of an AMI,[15] ER was significantly associated with an increased risk of a VT/VF occurrence or sudden death in the chronic phase of the AMI.

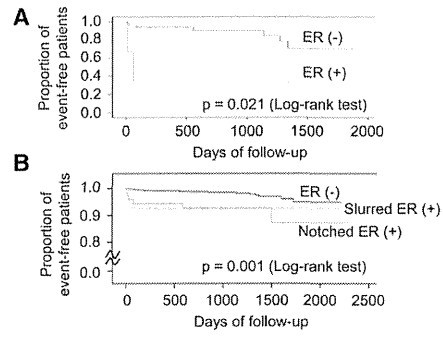

Figure 4. Kaplan–Meier curves. **A**, Kaplan–Meier curves in the patients with a left ventricular ejection fraction of <35%. Concomitant early repolarization was associated with an increased risk of sustained ventricular tachyarrhythmias or a sudden death occurrence in the patients with severe left ventricular dysfunction. **B**, Kaplan–Meier curve according to the morphology of the early repolarization (ER). Notched ER increased the occurrence of sustained ventricular tachyarrhythmia or sudden death (P=0.001 between the patients with a notched ER and those without ER; P=0.1 between the patients with a slurred ER and those without ER; and P=0.9 between the patients with a notched ER and those with slurred ER).

Proposed Mechanism of VT/VF in Patients With ER

In this study, in addition to severe left ventricular dysfunction and a high Killip class on admission, which have been reported as risk factors for the occurrence of VT/VF or sudden death during the chronic phase of an AMI,[22] to the best of our knowledge, we found for the first time that the presence of ER was a new risk factor for an event occurrence even after an adjustment for multiple variables.

Transmural differences in the early phases (phases 1 and 2) of the cardiac action potential, which are created by a disproportionate amplification of the repolarizing current in the epicardial myocardium because of an increase in the outward potassium currents mediated by the I_{to}, $I_{K\text{-}ATP}$, and $I_{K\text{-}Ach}$ channels, are considered to be responsible for the inscription of the ECG J wave.[23] The trigger and substrate for the development of phase 2 re-entry and VT/VF may eventually emerge from the transmural dispersion of the duration of the cardiac action potentials.[23] Patients who had a myocardial infarction have scar tissue in the myocardium that could become a substrate for ventricular tachycardia.[24] One possible speculation is that phase 2 re-entry and scar tissue play an important role in the development of sustained VT/VF as the trigger and substrate, respectively, resulting in the higher prevalence of an occurrence of VT/VF or sudden death in the chronic phase of an AMI in the patients with ER than in those without.

It is known that high-amplitude J-point elevation increases the risk of VF during the acute phase of an ST-elevation myocardial infarction.[25] J-point elevation at the onset of an ST-elevation myocardial infarction has been proposed to be due to the opening of the $I_{K\text{-}ATP}$ channels.[26] Our findings indicated that acquired ER was observed in 6 patients. We could speculate that persistent opening of the $I_{K\text{-}ATP}$ channels plays an important role in the presence of ER during the post-AMI phase.

Previous Studies

Previous studies have shown the characteristics of ER in those who have had VT/VF.[9–15] In the present study, ER in the inferior leads, high amplitude ER, a notched morphology, and ER without ST-segment elevation were associated with an increased risk of the occurrence of VT/VF or sudden death, which was similar to the findings of previous studies.[9–15] We could consider that these ER patterns indicated a malignant form.

Patel et al[14] showed that ER was the independent predictor of life-threatening VT/VF in patients with chronic coronary artery disease. All subjects of that study underwent an ICD implantation, and the mean ejection fraction was <30%. In the present study, however, the mean ejection fraction was 54%, and the prevalence of severe left ventricular dysfunction (ejection fraction <35%) and an ICD implantation was 5% and 3%, respectively. The present study showed for the first time that ER was associated with an increased risk of the

Table 2. Univariable and Multivariable Cox Proportional Regression Analyses of Ventricular Tachyarrhythmias or Sudden Death Occurrence

	Univariable		Multivariable	
Variables	Hazard Ratio (95% Confidence Interval)	*P* Value	Hazard Ratio (95% Confidence Interval)	*P* Value
Male sex	7.711 (1.045–56.916)	0.045		
Left anterior descending culprit artery	2.193 (0.977–4.922)	0.057		
Killip class on admission>I	3.319 (1.523–7.232)	0.003	2.746 (1.241–6.073)	0.013
Statin	0.476 (0.217–1.047)	0.065		
VT/VF occurrence within 48 h after AMI onset	3.625 (1.453–9.041)	0.006		
Left ventricular ejection fraction<35%	11.994 (5.342–26.932)	<0.001	11.829 (5.157–27.131)	<0.001
Early repolarization on the ECG obtained before discharge	4.234 (1.837–9.760)	0.001	5.370 (2.273–12.687)	<0.001

AMI indicates acute myocardial infarction; and VT/VF, ventricular tachyarrhythmia.

occurrence of VT/VF or sudden death >14 days after the onset of the AMI in not only patients with severe left ventricular dysfunction but also in those with mild to moderate left ventricular dysfunction.

Clinical Implications

Our study showed that the presence of ER increased the risk for the occurrence of VT/VF or sudden death in the chronic phase of an AMI in the patients who survived the first 14 days after an AMI. In particular, much attention should be paid to patients with ER in the inferior leads, high amplitude ER, a notching morphology of the ER, and ER without ST-segment elevation.

It is possible to underestimate the prevalence of ER on the ECG obtained shortly after the AMI onset because of the ST-T changes caused by the AMI itself, and in the present study, ER assessed on admission was not associated with the occurrence of VT/VF or sudden death. Therefore, the presence or absence of ER should be assessed from an ECG recorded at predischarge because acute ST-T elevation caused by the AMI itself sufficiently resolved about 10 days after the onset of the AMI.

Study Limitations

First, our study was a hypothesis-generating trial, not a conclusive trial, based on the retrospective design and relatively small number of end points. The small sample size limited the power of the study and was reflected in the broad CIs, most notably in the adjusted statistical analyses. Second, because the prevalence of an ICD implantation was only 1% in our study, we could have underestimated the occurrence of sustained VT/VF. Third, patients with an AMI are hospitalized for only 4 days in the United States.[27] It may be difficult to obtain an ECG 10 days post-AMI at predischarge in Western countries. Fourth, the use of β-blockers and statins was relatively low for the cohort given existing guidelines for post-AMI management. This fact may affect the increased risk of VT/VF or sudden death occurrence. Fifth, this study might miss the significance of ER presented in the precordial leads because the anterior precordial leads were excluded from the analysis of the ER. Therefore, further prospective studies with a larger sample size, long-term follow-up, and the participation of many hospitals and many countries may be needed to resolve these limitations and to confirm and enhance our results.

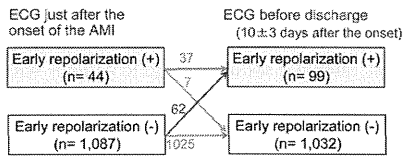

Figure 5. Time course of early repolarization. Changes in the early repolarization pattern between that just after the onset of an acute myocardial infarction (AMI) and that before hospital discharge.

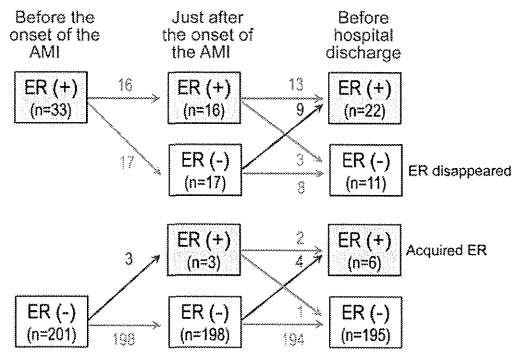

Figure 6. Time course of early repolarization (ER) in the 234 patients whose ECG obtained before the AMI onset could be assessed. Changes in the ER pattern among that before the onset of an acute myocardial infarction (AMI), just after the onset of the AMI, and that before hospital discharge.

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Disclosures

None.

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CLINICAL PERSPECTIVE

We recently showed that the presence of early repolarization (ER) increases the risk of ventricular fibrillation occurrences in the early phase of an acute myocardial infarction (AMI). The purpose of this study was to clarify whether the presence of ER in the ECG recorded at a mean of 10 days post-AMI is associated with the occurrences of ventricular tachyarrhythmia or sudden death in the chronic phase of an AMI. In the present study, in addition to an left ventricular ejection fraction of <35% and Killip class of >I, which have been reported as risk factors for ventricular tachyarrhythmia or sudden death during the chronic phase of an AMI, we demonstrated for the first time that the presence of ER was a new risk factor for the occurrence of ventricular tachyarrhythmia or sudden death even after adjustment for multivariables. In particular, attention should be paid to patients with ER in the inferior leads, high-amplitude ER, a notching morphology of the ER, and ER without ST-segment elevation. It is possible to underestimate the prevalence of ER on the ECG obtained shortly after the AMI onset because of the ST-T changes caused by the AMI itself; ER assessed on admission was not associated with the occurrence of ventricular tachyarrhythmia or sudden death in the present study. Therefore, the presence or absence of ER should be assessed from an ECG recorded at a mean of 10 days post-AMI. Further prospective validation is necessary to confirm and enhance these findings.

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Early Repolarization Increases the Occurrence of Sustained Ventricular Tachyarrhythmias and Sudden Death in the Chronic Phase of an Acute Myocardial Infarction

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Effect of Flecainide on T-wave Alternans in Andersen-Tawil Syndrome

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Abbreviations: ECG, electrocardiogram; PVC, premature ventricular contraction; HR, heart rate

Introduction

Andersen-Tawil syndrome is a heterogeneous disorder characterized by periodic paralysis, ventricular arrhythmias, QT prolongation, craniofacial dysmorphic features, and autosomal dominant inheritance. Most patients have a mutation in the ion channel gene, *KCNJ2*, which encodes the inward rectifier K^+ channel Kir2.1, a component of the inward rectifier I_{K1}. T-wave alternans, defined as a beat-to-beat change in the amplitude and/or shape on the electrocardiogram (ECG), has been reported as a presage of life-threatening events. Nowadays, measurement of microvolt-level T-wave alternans that reflects a quantifiable, fundamental electrophysiologic property linked to life-threatening ventricular arrhythmias is a feasible procedure in clinical practice. However, it is not known that T-wave alternans is associated with ventricular arrhythmia in Andersen-Tawil syndrome. It was reported that flecainide was effective in suppressing ventricular tachyarrhythmia in Andersen-Tawil syndrome.[1-3] Therefore, we evaluated the effects of flecainide on T-wave alternans and ventricular arrhythmia in this syndrome.

Case presentation

Here we report a case of Andersen-Tawil syndrome whose exercise-induced T-wave alternans was almost suppressed by oral administration of flecainide. A 22-year-old man was introduced to the cardiology clinic of our university hospital because of change of residence. He was diagnosed as Andersen-Tawil syndrome at the age of 18 years. His height was 63.8 inches; his weight, 117 pounds. Physical examination on the chest was unremarkable. He has a family history of Andersen-Tawil syndrome in his younger sister who suffered from periodic paralysis and had QT prolongation. This patient did not have any symptoms relating to Andersen-Tawil syndrome. The gene analysis of this case revealed a mutation (c.200G>A p.R67Q) in *KCNJ2*.

He had been treated with atenolol (50 mg/day) and mexiletine (200 mg/day). To test

the effects of flecainide, mexiletine was taken off. One month after the discontinuation of administration of mexiletine, 12-lead ECG recording, treadmill exercise test, and 24-hour ambulatory ECG recording were performed with use of atenolol (50 mg/day) alone. A 12-lead ECG showed a sinus rhythm and prolonged QT interval (Figure 1A). Frequent premature ventricular contractions (PVCs) were present. Although most PVCs arose during the period of U wave with the coupling interval of 520 ms, one PVC (asterisk) emerged from the baseline level. Treadmill exercise test was carried out according to a standard Bruce protocol. The number of PVCs progressively increased, as heart rate (HR) increased from 2 min after the exercise began (Figure 1B). However, the alteration of the number of PVCs did not parallel correspond to the increase in HR: i.e., it gradually decreased after the exercise continued for 10 min and finally PVC rarely occurred from 12 min after the exercise initiation. The quantification of microvolt T-wave alternans was obtained when the PVCs diminished during the exercise testing. T-wave alternans was assessed based on the time-domain modified moving average analysis using commercially available software (GE Healthcare Medical Systems, Milwaukee, WI, USA). The amplitude of T-wave alternans was 243 μV in lead V_5, when HR was 160 beats/min (Figure 1C). Twenty four-hour ambulatory ECG recording revealed that PVCs were frequently present: the total number of PVCs, 19,389/day; couplet PVCs, 2,964/day; triplet PVCs, 91/day; and non-sustained ventricular tachycardia, 4 times/day. After these tests were completed, flecainide (100 mg/day) was administered in addition to atenolol (50 mg/day).

One month after atenolol and flecainide were administered, 12-lead ECG recording, treadmill exercise test, and 24-hour ambulatory ECG recording were repeated. Twelve-lead ECG showed a sinus rhythm of 48 beats/min and no PVC (Figure 2A). QT interval shortened to 440 ms, and corrected QT interval by Bazett's formula was 391 ms. During treadmill exercise testing, PVCs rarely occurred (Figure 2B), although the HR response to exercise was identical to that of the previous treadmill exercise test. T-wave alternans was almost