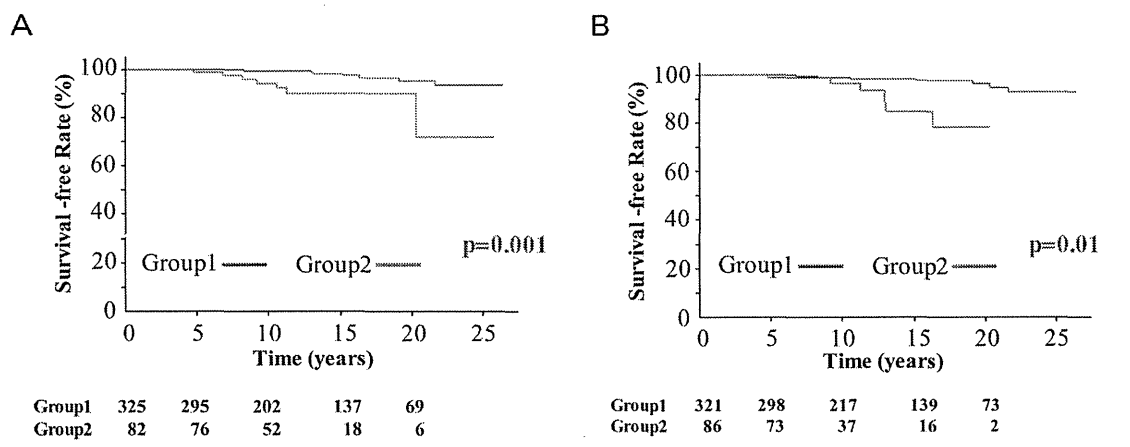

Figure 2. Kaplan-Meier survival analysis for cardiovascular mortality. (A) QRS-duration incremental rate <5 ms/year (Group 1) vs. ≥5 ms/year (Group 2). (B) PR-interval incremental rate <4 ms/year (Group 1) vs. ≥4 ms/year (Group 2). Numbers of subjects at risk are shown under each graph.

Table 4. Univariate and Multivariate Survival Analyses of Cardiovascular Mortality

	Univariate analysis (n=407)		Multivariate analysis (n=407)*		Multivariate analysis except nodal-blocking drugs (n=337)†	
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)
Age (<61 years=1)	0.10	2.44 (0.86–7.50)	0.30	1.82 (0.59–5.95)	0.97	1.02 (0.27–3.92)
Sex (female=1)	0.17	2.56 (0.71–16.37)	0.16	2.72 (0.71–18.00)	0.49	1.81 (0.37–14.13)
Heart rate (<66 beats/min=1)	0.98	1.01 (0.35–2.82)	0.54	0.71 (0.23–2.13)	0.67	1.34 (0.34–5.41)
Incremental rate of QRS duration (<5 ms/year=1)	0.004	5.04 (1.72–14.49)	0.06	3.18 (0.95–10.61)	0.03	4.31 (1.19–16.50)
Incremental rate of PR interval (<4 ms/year=1)	0.005	5.63 (1.76–17.62)	0.17	2.39 (0.69–8.21)	0.02	6.90 (1.47–36.96)

*Adjusted for age, sex, heart rate, LBBB, arrhythmias except AF, incremental rate of QRS duration, incremental rate of PR interval, diabetes mellitus, and cardiomyopathy.
†Adjusted for age, sex, heart rate, arrhythmias except AF, incremental rate of QRS duration, incremental rate of PR interval, and cardiomyopathy.
Abbreviations as in Tables 1–3.

the ECG characteristics. In the first ECG, heart rate, PR interval, and QRS duration did not differ between patients with and without cardiovascular death. The prevalence of LBBB was significantly higher in patients with cardiovascular death than in those without; but the prevalence of other abnormal intraventricular conductions did not differ between the 2 groups. The temporal increase in PR interval and the incremental rate of PR interval were significantly greater in patients with cardiovascular death than in those without. The temporal increase in QRS duration was not significantly different between patients with and without cardiovascular death, but the incremental rate of QRS duration was significantly higher in patients with cardiovascular death than in those without.

Long-term prognosis was analyzed after excluding patients who developed AF and second- or third-degree atrioventricular block, being evaluated in 407 patients. In **Figure 2**, the Kaplan-Meier estimates of the probability of freedom from cardiovascular mortality indicate that the temporal incremental rate of QRS duration of 5 ms/year or greater was associated with a significantly increased risk of cardiovascular mortality than that of <5 ms/year (HR, 5.0; 95% CI, 1.72–14.49; P=0.004) (**Figure 2A**). The temporal incremental rate of PR interval of 4 ms/year or greater was associated with a significantly increased risk of cardiovascular mortality than that of <4 ms/year (HR, 5.6; 95% CI, 1.76–17.62; P=0.005) (**Figure 2B**). **Table 4** shows the univariate and multivariate survival analyses in association with cardiovascular death. The temporal incremental rate of QRS duration and PR interval was significantly associated with cardiovascular mortality after exclusion of nodal-blocking drugs. Both ECG variables were independent of age, sex, and heart rate. Confounding diseases were not associated with cardiovascular mortality.

All-Cause Mortality A total of 59 patients (12.9%) died during the follow-up: 16 from cardiovascular death as noted earlier, 24 from malignant disorders, 6 from severe infection, and 13 from other causes. At baseline, age was significantly higher in patients with all-cause death than in those without (63.4±10.8 vs. 57.1±15.0 years; P=0.002), but the sex prevalence was not significantly different between the 2 groups (80% vs. 74% male; P=0.32). The prevalences of cardiomyopathy and malignant disease were significantly higher in patients with all-cause death than in those without (P<0.05 for each), but the prevalences of ischemic heart disease, valvular heart disease, diabetes, and AF were not significantly different

Table 5. Univariate and Multivariate Analyses of All-Cause Death

	Univariate analysis (n=407)		Multivariate analysis (n=407)*		Multivariate analysis except nodal-blocking drugs (n=337)†	
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)
Age (<61 years=1)	<0.0001	3.40 (1.89–6.35)	0.0002	3.36 (1.76–6.65)	0.01	2.64 (1.30–5.47)
Sex (female=1)	0.44	1.28 (0.69–2.56)	0.32	1.40 (0.73–2.84)	0.17	1.68 (0.81–3.84)
Heart rate (<66 beats/min=1)	0.50	1.21 (0.70–2.11)	0.39	1.29 (0.72–2.32)	0.52	1.24 (0.65–2.37)
Incremental rate of QRS duration (<5 ms/year=1)	0.004	2.59 (1.38–4.66)	0.05	1.95 (0.99–3.66)	–	–
Incremental rate of PR interval (<4 ms/year=1)	0.003	2.92 (1.48–5.49)	0.39	1.37 (0.65–2.75)	0.15	1.87 (0.79–4.19)
Malignant disease (no malignancy=1)	0.004	4.09 (1.65–8.78)	0.02	3.27 (1.25–7.47)	0.02	4.03 (1.41–9.97)

*Adjusted for age, sex, heart rate, AF, nodal-blocking drugs, incremental rate of QRS duration, incremental rate of PQ interval, cardiomyopathy, and malignant disease.
†Adjusted for age, sex, heart rate, incremental rate of PQ interval, cardiomyopathy, and malignant disease.
Abbreviations as in Tables 1,3.

between the 2 groups. The follow-up period was marginally different between patients with and without all-cause death (11.8±5.9 vs. 13.5±6.4 years, P=0.05). **Table S3** shows the ECG characteristics. In the baseline ECG, heart rate, PR interval, and QRS duration was not significantly different between patients who died and those who survived. The prevalence of abnormal intraventricular conduction was not significantly different between patients who died and survived. The temporal increase in PR interval and the incremental rate of PR interval was not significantly different between patients who died and those who survived. The temporal increase in QRS duration was not significantly different between patients who died and those who survived, but the incremental rate of QRS duration was significantly higher in patients who died than in those who survived.

Long-term prognosis was analyzed after excluding the patients who developed AF and second- or third-degree atrioventricular block, being evaluated in 407 patients. **Table 5** shows the univariate and multivariate survival analyses in association with all-cause death. Advanced age and malignant diseases were independently associated with all-cause mortality even after exclusion of nodal-blocking drugs. Neither the temporal incremental rate of QRS duration nor the temporal incremental rate of PR interval was independently associated with cardiovascular mortality. In addition, sex, heart rate, and confounding diseases except malignancy were not associated with all-cause mortality.

Discussion

Historically, in the 19th century Adams and Stokes separately reported a patient who suffered fainting episodes with slow pulse rate. Congenital heart block and familial occurrence of atrioventricular conduction block were subsequently noted,[8,9] suggesting inherited conduction disorders. PCCD was initially reported as an electrical conduction disorder.[10] Familial clustering of conduction system degeneration has led to the discovery of novel mutations resulting in PCCD in the absence of structural heart disease.[11] To date, multiple molecular defects responsible for PCCD have been found.[12] In addition, congenital heart diseases are accompanied by functional abnormalities of the conduction system,[13] and overlap of PCCD with structural heart diseases such as cardiomyopathy has been reported.[14,15] Neuromuscular disorders are also associated with the development of PCCD.[16] Taken together, PCCD appears not to be a single clinical entity caused by a single-gene mutation. We expand the concept of PCCD to include various cardiac diseases. In our large hospital-based population, the major findings of PCCD are summarizes as follows: (1) the temporal incremental rate of PR interval was independently associated with increased risk of HF hospitalization and cardiovascular mortality, (2) the temporal incremental rate of QRS duration was independently associated with increased risk of HF hospitalization and cardiovascular mortality, and thus (3) the severity of PCCD was intimately associated with an adverse prognosis.

Pathophysiology of PCCD

The cardiac impulse originating from the sinus node activates the atria and the ventricle, with the specialized conduction system depolarized first and the working myocardium secondarily depolarized. For impulse propagation in both the atrium and ventricle, the voltage-gated sodium channel and gap junctions are of major importance, because the former determines the excitability of the cells and the latter serves as the depolarizing current transmitted from cell to cell. Lev and Unger[1] and Lenègre[2] reported the association of excessive interstitial fibrosis near and in the specialized conduction system with PR-interval prolongation and QRS-duration widening in postmortem examinations. Their findings suggested that interstitial fibrosis played a significant role in activation delay in patients with PCCD. Familial clustering of cardiac conduction disturbance, which occur in the absence of structural heart disease or systemic disease, results from mutations in cardiac ion channel genes and associated or modifying proteins such as cytoskeletal proteins. The SCN5A mutation that results in nonfunctional human cardiac sodium channels has been found in familial PCCD.[17] This mutation consequently gives rise to slowing cardiac conduction. Besides, SCN5A has been reported as associated with dilated cardiomyopathy.[15] Therefore, structural and functional PCCDs may share the same pathophysiological background. The temporal incremental rate of QRS duration may correlate with deterioration of ventricular function, leading to increased LV filling pressures and consequently myocardial ischemia. Such longstanding conditions also may result in subendocardial fibrosis.[18] Thus, progressive widening of the QRS duration could be a surrogate for perpetual deterioration of the LV. Consistent with these pathophysiological mechanisms, the major outcome of this study was HF hospitalization.

Although most reports dealing with PCCD have consisted of small groups of patients, the presence of mutations in the

SCN5A, PRKAG2, NKX2-5 and LMNA genes, which were found to be linked to cardiomyopathies, conduction disease, and ventricular arrhythmias, has been investigated. Inter- and intraventricular conduction disturbances are the most common ECG pattern preceding the development of complete heart block, particularly in the presence of structural heart disease. Recently, it was reported that gain-of-function mutations in *TRPM4* encoding a calcium-activated nonselective cation channel of the transient receptor potential melastatin (TRPM) ion channel cause autosomal dominant isolated cardiac conduction disease.[19] In the present study, the temporal deterioration in supraventricular and ventricular conduction was independently associated with a worse prognosis of PCCD. Although gene analysis was not performed in this study, further investigation is needed to clarify whether gene mutation exists to stratify the risk of PCCD in our cohort.

Prognosis

General Population In the Framingham study,[20] the prevalence of BBB was related to aging and was more common among men than among women. Some studies report that there is no significant relation between BBB and mortality in the general population.[21–24] Regarding newly occurred BBB, left BBB was associated with an increased risk of developing overt cardiovascular disease and increased cardiac mortality.[25,26] These studies suggest that progressive degeneration of the cardiac myocardium might coincide with the development of BBB.

Medical Population In the medical population, prolonged QRS duration is reported to be a significant and independent predictor of cardiovascular mortality.[4] Several studies have shown that both left and right BBB are associated with increased mortality among patients with structural heart diseases.[27–29] In myocardial infarction, patients with BBB presented significantly more often with congestive HF and higher mortality than do their counterparts without BBB.[30] Prolonged QRS duration is also associated with decreased left ventricular systolic function and poor prognosis in patients with coronary artery disease.[6] These studies indicate that QRS duration matters a great deal for the prognosis of patients with cardiovascular diseases.

Though the follow-up period was not long, serial ECG recordings have revealed that an increase in QRS duration is associated with adverse outcomes in patients with HF.[31,32] Biventricular pacing therapy for HF that corrected the mechanical dyssynchrony caused by ventricular conduction disturbance provides evidence that patients with prolonged QRS duration have a higher susceptibility to improving their physical status by cardiac resynchronization therapy.[33] Along with these studies, the present study elucidated that the temporal incremental rate of QRS duration was independently associated with long-term poor prognosis. In addition, this study underscored the independent association between the temporal incremental rate of PR interval and QRS duration. Patients who developed AF during the follow-up were not enrolled in this study, because serial change in the PR interval was not able to be measured in those patients. Therefore, the results of this study might underestimate the prognosis of PCCD, because AF can be regarded as advanced stage of atrial conduction delay.

In this hospital-based cohort, the endpoints were determined by analysis of detailed medical records in which the prognostic outcomes were identified according to ICD codes, so our data were reliable during the long-term follow-up period. In addition, medical records are useful for evaluating physical conditions not only at 1 time point but also during follow-up, thus we precisely reviewed the medical records of all patients enrolled throughout the follow-up period.

Study Limitations

Because this cohort study was not prospectively conducted using ECG recordings, several limitations are inherent. First, we determined the increase of the PR interval and QRS duration by averaging their temporal variations. Those increases might not be temporally constant. To avoid excess change during a short time, we used ECGs for which the recording interval was more than 1 year. Second, the temporal increment rate of the PR interval was a few milliseconds. Although the temporal increment rate of the PR interval was used to stratify the prognostic outcomes, the effect of autonomic tone on the PR interval was not negligible. Third, intermittent BBB might have been missed unless the ECG finding was recorded in the hospital. Because no intermittent BBB could be documented during the follow-up in patients enrolled in this study, it is thought that intermittent BBB rarely occurred in this hospital-based population. Fourth, we did not involve cardiac functions such as left ventricular ejection fraction and mitral regurgitation. Lastly, because our study included patients who underwent ECG recording in our hospital, the risk of HF hospitalization in the study population undoubtedly was greater than that in the general population. Therefore, this factor should be considered when our results are extrapolated to a broader population.

Study Implications

PCCD was primarily identified as a cardiac electrical disease representing temporal prolongation of the QRS duration. Although prolonged QRS duration is known to be associated with adverse prognosis, the prognosis of PCCD remains unclear in a large population. This study demonstrated that patients with a higher degree of PCCD have a worse prognosis. The independent relationship between PCCD and HF hospitalization and between PCCD and cardiovascular mortality helps find patients who are at risk. The increased risk of HF hospitalization associated with the temporal incremental rate of QRS duration suggests a possible role for cardiac resynchronization therapy, particularly among patients with systolic HF. Therefore, our results indicate that careful follow-up of the ECG deserves attention for determining which patients are most likely to benefit from preventive HF therapy such as diuretics. For example, when patients visit cardiology clinics, repetitive ECG recordings might provide a noninvasive means of identifying those at high risk for worsening of HF. To make the temporal variation of the PR interval and QRS duration clinically available for treatment of patients at the early stage, improvements in the software for automatic display of these ECG variables are needed.

Acknowledgments

The authors thank Seiichi Fujisaki, Akihiko Ejima, and Tatsumi Uchiyama (GE Yokokawa Medical System Co) for their technical assistance.

Disclosures

None.

References

1. Lev M, Unger PN. The pathology of the conduction system in acquired heart disease. I: Severe atrioventricular block. *AMA Arch Pathol* 1955; **60:** 502–529.
2. Lenegre J. Etiology and pathology of bilateral bundle branch block

in relation to complete heart block. *Prog Cardiovasc Dis* 1964; **6:** 409–444.
3. Holm H, Gudbjartsson DF, Arnar DO, Thorleifsson G, Thorgeirsson G, Stefansdottir H, et al. Several common variants modulate heart rate, PR interval and QRS duration. *Nat Genet* 2010; **42:** 117–122.
4. Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S, Froelicher VF. Prognostic significance of quantitative QRS duration. *Am J Med* 2006; **119:** 600–606.
5. Bode-Schnurbus L, Bocker D, Block M, Gradaus R, Heinecke A, Breithardt G, et al. QRS duration: A simple marker for predicting cardiac mortality in ICD patients with heart failure. *Heart* 2003; **89:** 1157–1162.
6. Murkofsky RL, Dangas G, Diamond JA, Mehta D, Schaffer A, Ambrose JA. A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction [see Comment]. *J Am Coll Cardiol* 1998; **32:** 476–482.
7. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346:** 877–883.
8. Trevino AJ, Beller BM. Conduction disturbances of the left bundle branch system and their relationship to complete heart block. II: A review of differential diagnosis, pathology and clinical significance. *Am J Med* 1971; **51:** 374–382.
9. Schaal SF, Seidensticker J, Goodman R, Wooley CF. Familial right bundle-branch block, left axis deviation, complete heart block, and early death: A heritable disorder of cardiac conduction. *Ann Intern Med* 1973; **79:** 63–66.
10. Smits JP, Veldkamp MW, Wilde AA. Mechanisms of inherited cardiac conduction disease. *Europace* 2005; **7:** 122–137.
11. Benson DW, Wang DW, Dyment M, Knilans TK, Fish FA, Strieper MJ, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest* 2003; **112:** 1019–1028.
12. Wolf CM, Berul CI. Inherited conduction system abnormalities: One group of diseases, many genes. *J Cardiovasc Electrophysiol* 2006; **17:** 446–455.
13. Schott JJ, Benson DW, Basson CT, Pease W, Silberbach GM, Moak JP, et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. *Science* 1998; **281:** 108–111.
14. Nguyen TP, Wang DW, Rhodes TH, George AL Jr. Divergent biophysical defects caused by mutant sodium channels in dilated cardiomyopathy with arrhythmia. *Circ Res* 2008; **102:** 364–371.
15. Wilde AA, Brugada R. Phenotypical manifestations of mutations in the genes encoding subunits of the cardiac sodium channel. *Circ Res* 2011; **108:** 884–897.
16. Bonne G, Di Barletta MR, Varnous S, Becane HM, Hammouda EH, Merlini L, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet* 1999; **21:** 285–288.
17. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, et al. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet* 1999; **23:** 20–21.
18. Aoki T, Fukumoto Y, Sugimura K, Oikawa M, Satoh K, Nakano M, et al. Prognostic impact of myocardial interstitial fibrosis in non-ischemic heart failure: Comparison between preserved and reduced ejection fraction heart failure. *Circ J* 2011; **75:** 2605–2613.
19. Liu H, El Zein L, Kruse M, Guinamard R, Beckmann A, Bozio A, et al. Gain-of-function mutations in TRPM4 cause autosomal dominant isolated cardiac conduction disease. *Circ Cardiovasc Genet* 2010; **3:** 374–385.
20. Kreger BE, Anderson KM, Kannel WB. Prevalence of intraventricular block in the general population: The Framingham study. *Am Heart J* 1989; **117:** 903–910.
21. Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: The study of men born 1913. *Circulation* 1998; **98:** 2494–2500.
22. Fleg JL, Das DN, Lakatta EG. Right bundle branch block: Long-term prognosis in apparently healthy men. *J Am Coll Cardiol* 1983; **1:** 887–892.
23. Liao YL, Emidy LA, Dyer A, Hewitt JS, Shekelle RB, Paul O, et al. Characteristics and prognosis of incomplete right bundle branch block: An epidemiologic study. *J Am Coll Cardiol* 1986; **7:** 492–499.
24. Fahy GJ, Pinski SL, Miller DP, McCabe N, Pye C, Walsh MJ, et al. Natural history of isolated bundle branch block. *Am J Cardiol* 1996; **77:** 1185–1190.
25. Schneider JF, Thomas HE Jr, Kreger BE, McNamara PM, Kannel WB. Newly acquired left bundle-branch block: The Framingham study. *Ann Intern Med* 1979; **90:** 303–310.
26. Schneider JF, Thomas HE, Kreger BE, McNamara PM, Sorlie P, Kannel WB. Newly acquired right bundle-branch block: The Framingham study. *Ann Intern Med* 1980; **92:** 37–44.
27. Hindman MC, Wagner GS, JaRo M, Atkins JM, Scheinman MM, DeSanctis RW, et al. The clinical significance of bundle branch block complicating acute myocardial infarction. 1: Clinical characteristics, hospital mortality, and one-year follow-up. *Circulation* 1978; **58:** 679–688.
28. Ricou F, Nicod P, Gilpin E, Henning H, Ross J Jr. Influence of right bundle branch block on short- and long-term survival after acute anterior myocardial infarction. *J Am Coll Cardiol* 1991; **17:** 858–863.
29. Hesse B, Diaz LA, Snader CE, Blackstone EH, Lauer MS. Complete bundle branch block as an independent predictor of all-cause mortality: Report of 7,073 patients referred for nuclear exercise testing. *Am J Med* 2001; **110:** 253–259.
30. Melgarejo-Moreno A, Galcera-Tomas J, Garcia-Alberola A, Valdes-Chavarri M, Castillo-Soria FJ, Mira-Sanchez E, et al. Incidence, clinical characteristics, and prognostic significance of right bundle-branch block in acute myocardial infarction: A study in the thrombolytic era. *Circulation* 1997; **96:** 1139–1144.
31. Shamim W, Yousufuddin M, Cicoria M, Gibson DG, Coats AJ, Henein MY. Incremental changes in QRS duration in serial ECGs over time identify high risk elderly patients with heart failure. *Heart* 2002; **88:** 47–51.
32. Grigioni F, Carinci V, Boriani G, Bracchetti G, Potena L, Magnani G, et al. Accelerated QRS widening as an independent predictor of cardiac death or of the need for heart transplantation in patients with congestive heart failure. *J Heart Lung Transplant* 2002; **21:** 899–902.
33. Moss AJ. What we have learned from the family of multicenter automatic defibrillator implantation trials. *Circ J* 2010; **74:** 1038–1041.

Supplementary Files

Supplementary File 1

Figure S1. Temporal alterations of 12-lead ECGs in a patient with progressive cardiac conduction disease (PCCD).

Table S1. Comparison of Baseline ECG and Follow-up ECG According to Heart Failure Hospitalization

Table S2. Comparison of Baseline ECG and Follow-up ECG According to Cardiovascular Death

Table S3. Comparison of Baseline ECG and Follow-up ECG According to All-Cause Death

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-12-0849

Images and Case Reports in Arrhythmia and Electrophysiology

Successful Catheter Ablation of Bidirectional Ventricular Premature Contractions Triggering Ventricular Fibrillation in Catecholaminergic Polymorphic Ventricular Tachycardia With *RyR2* Mutation

Takashi Kaneshiro, MD; Yoshihisa Naruse, MD; Akihiko Nogami, MD; Hiroshi Tada, MD; Kentaro Yoshida, MD; Yukio Sekiguchi, MD; Nobuyuki Murakoshi, MD; Yoshiaki Kato, MD; Hitoshi Horigome, MD; Mihoko Kawamura, MD; Minoru Horie, MD; Kazutaka Aonuma, MD

The subject of this report is a 38-year-old woman who often experienced syncope since childhood. Syncope occurred >10 times a year and was associated with convulsion during exercise and emotionally exciting situations. The patient's 13-year-old daughter had also experienced frequent episodes of syncope and developed ventricular fibrillation (VF) during treadmill exercise testing that was successfully defibrillated with electric shock. Witnessing this situation, the patient also lost consciousness, with documented VF that was converted to sinus rhythm by cardiopulmonary resuscitation without electric defibrillation.

Both the patient and her daughter were admitted to our hospital. We performed echocardiography, coronary angiography, and cardiac CT, the results of which revealed no structural heart disease. Resting 12-lead ECG did not indicate any abnormalities, including long-QT syndrome or Brugada syndrome. A signal-averaged ECG revealed no late potentials. Treadmill exercise testing easily induced bigeminal ventricular premature contractions (VPCs) with a right bundle branch block configuration and inferior axis (Figure 1A), and the exercise was terminated because of intolerable symptoms. Catecholamine stress test was started with administration of continuous intravenous infusion of epinephrine in a stepwise manner from 0.025 μg/kg per minute.[1] During epinephrine infusion at a rate of 0.1 μg/kg per minute, multifocal VPCs (VPC #1, right bundle branch block configuration and superior axis; VPC #2, right bundle branch block configuration and inferior axis [the same VPC configuration as that induced during the treadmill exercise testing]; and VPC #3, left bundle branch block configuration and inferior axis) appeared, and VPC #1 following VPC #2 subsequently induced VF (Figure 1B).

Administration of bisoprolol 5 mg QD was given but failed to suppress the exercise-induced bigeminal VPCs with the same morphology as induced previously. Because frequent deliveries of shock were believed to be likely, even with β-blocker treatment, catheter ablation was offered to the patient before implantable cardioverter-defibrillator (ICD) implantation. Catheter mapping and ablation for the bidirectional VPCs were performed with a 3D electroanatomic mapping system (CARTO; Biosense Webster) and a 3.5-mm-tip irrigation catheter (NaviStar; Thermo Cool) with only local anesthesia. No VPCs, ventricular tachycardia (VT), or VF were inducible with burst pacing and programmed stimulation from both right ventricular apex and right outflow tract during baseline and continuous intravenous infusion of isoproterenol.

With epinephrine infusion at a rate of 0.1 μg/kg per minute, VPC #1 and VPC #2 appeared. VPC #1 was nonsustained, and a presystolic Purkinje potential was recorded at the left ventricular inferoseptal area near the posteromedial papillary muscle, which preceded the onset of VPC #1 by 18 ms. The unipolar electrogram from the ablation catheter during VPC #1 showed a QS pattern, and a perfect match of the QRS configuration was obtained by pace mapping (Figure 2). Radiofrequency energy application to this site provoked some ventricular acceleration beats, and several radiofrequency energy applications around the target site finally eliminated all the VPCs, resulting in complete suppression of all VPC #1.

After the ablation of VPC #1, isolated occurrences of VPC #2 continued, and a local bipolar electrogram recorded on the left coronary cusp showed discrete prepotential that preceded the onset of VPC #2 by 65 ms, and a perfect match of the

Received July 26, 2011; accepted January 5, 2012.

From the Cardiovascular Division, Institute of Clinical Medicine (T.K., Y.N., H.T., K.Y., Y.S., N.M., K.A.) and Department of Child Health (Y.K., H.H.), Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan; Division of Heart Rhythm Management, Yokohama Rosai Hospital, Yokohama, Japan (A.N.); and Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Shiga, Japan (M.K., M.H.).

Correspondence to Kazutaka Aonuma, MD, Cardiovascular Division, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. E-mail kaonuma@md.tsukuba.ac.jp

(*Circ Arrhythm Electrophysiol.* **2012;5:e14-e17.**)

© 2012 American Heart Association, Inc.

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.111.966549**

Downloaded from circep.ahajournals.org at KHAO PUBLICATIONS on February 24, 2013

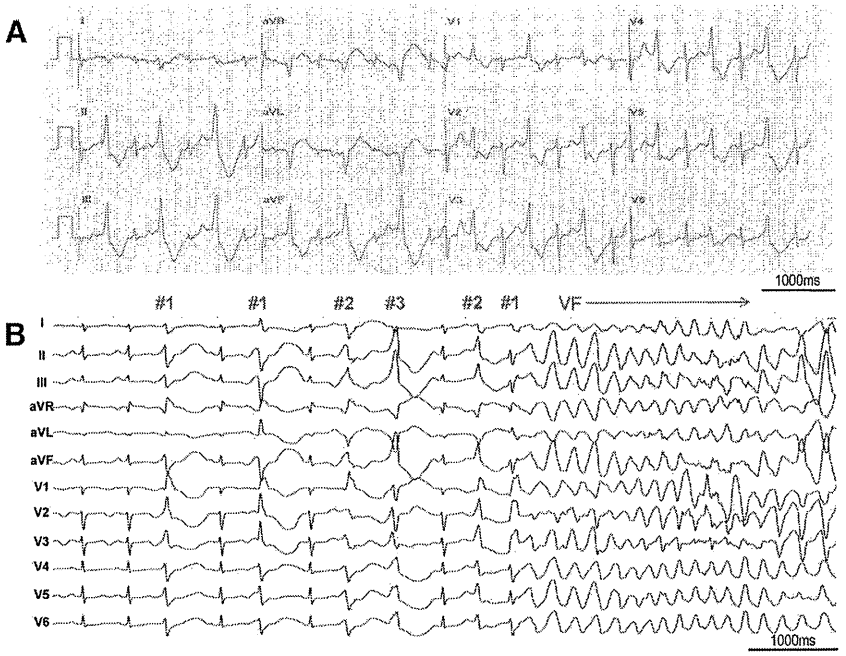

Figure 1. A, Twelve-lead ECG recording during treadmill exercise testing. Bigeminal ventricular premature contractions (VPCs) appeared during the second stage of the Bruce protocol. VPC morphology represented a right bundle branch block configuration and inferior axis. Because the patient experienced intolerable symptoms, the test was discontinued. **B**, Epinephrine stress test. Continuous intravenous infusion of epinephrine was started from a rate of 0.025 μg/kg per minute, and the QT interval did not changed. At a rate of 0.1 μg/kg per minute, VPC #1 (right bundle branch block configuration and superior axis), VPC #2 (right bundle branch block configuration and inferior axis, same as that induced in the treadmill exercise testing), and VPC #3 (left bundle branch block configuration and inferior axis) were induced. Subsequently, VPC #1 following VPC #2 suddenly induced ventricular fibrillation, which was successfully terminated with electric shock.

QRS configuration was obtained by pace mapping (Figure 3). Radiofrequency energy application to the left coronary cusp abolished VPC #2 4 s after the onset of radiofrequency energy application. After successful catheter ablation of bidirectional VPCs, neither VPCs nor VF were inducible, even with an infusion of epinephrine of up to 1.2 μg/kg per minute (a >10 times higher dose than provocation). Precise ablation sites in a 3D electroanatomic mapping merged with contrast-enhanced CT are shown in Figure 4.

ICD implantation was performed, and the patient was discharged from the hospital on bisoprolol 2.5 mg QD. Serial Holter ECGs after the ablation showed only 3 to 5 isolated VPCs with a different morphology from the previously observed VPCs, and treadmill exercise testing induced no VPCs at the maximal workload. During 16-month follow-up, neither episodes of syncope nor ICD therapy occurred. Genetic analysis revealed a mutation in the ryanodine receptor gene (*RyR2*), and a diagnosis of catecholaminergic polymorphic VT (CPVT) was confirmed (Figure 5).[2] The patient's daughter was also given a diagnosis of CPVT with same mutation in *RyR2* and had catheter ablation for the origins of bidirectional VT. Although she refused ICD

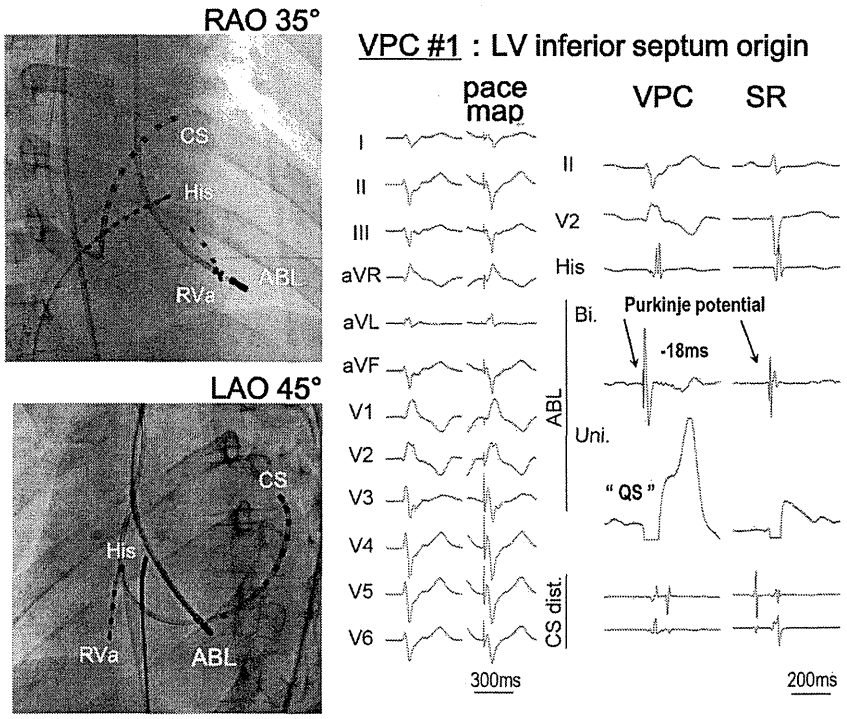

Figure 2. Activation mapping and pace mapping for VPC #1. A Purkinje potential was recorded from the left ventricular inferoseptum and preceded the QRS onset by 18 ms. The unipolar electrogram recorded from the distal electrode showed a QS pattern. Perfect pace mapping was obtained at this site. ABL indicates ablation catheter; CS, coronary sinus; His, His bundle; LAO, left anterior oblique; RAO, right anterior oblique; RVa, right ventricular apex; SR, sinus rhythm; VPC, ventricular premature contraction.

Downloaded from circep.ahajournals.org at KITAO PUBLICATIONS on February 24, 2013

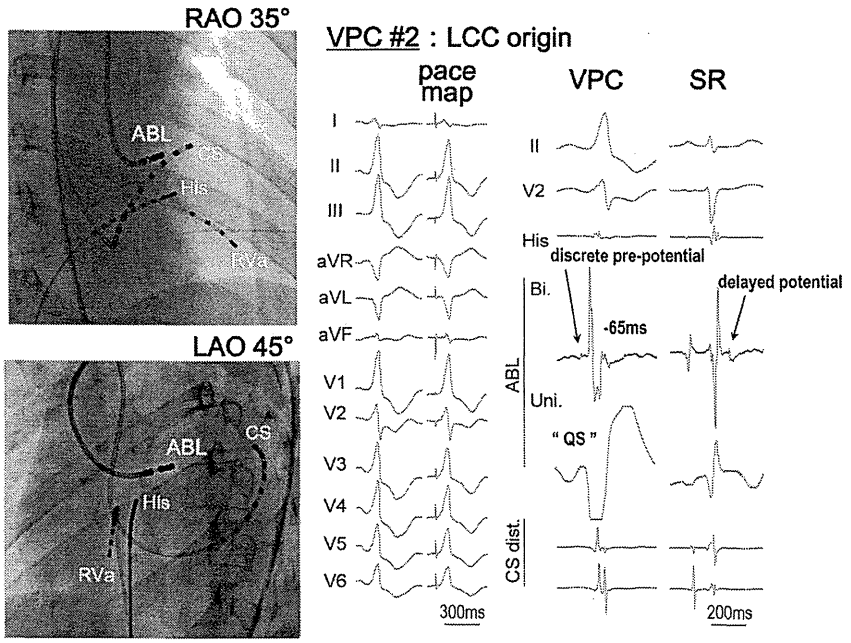

Figure 3. Activation mapping and pace mapping for VPC #2. A local bipolar electrogram recorded from the LCC showed a discrete prepotential that preceded the QRS onset by 65 ms associated with a QS pattern of unipolar electrogram. Perfect pace mapping was obtained at this site. ABL indicates ablation catheter; CS, coronary sinus; His, His bundle; LAO, left anterior oblique; LCC, left coronary cusp; RAO, right anterior oblique; RVa, right ventricular apex; SR, sinus rhythm; VPC, ventricular premature contraction.

implantation, she had not experienced any episode of VT or syncope with β-blocker treatment.

The generally accepted therapy for CPVT has been β-blockers,[3] and the additional administration of flecainide or verapamil to β-blockers has been reported to be effective; however, the effects of those drugs are not fully standardized. For medically refractory cases, sympathetic denervation is one of the alternative treatment options. The ICD is considered the definitive therapy for the prevention of sudden cardiac death; however, failure to prevent sudden cardiac death has been reported in several cases because ICD shock delivery might lead to catecholamine release, resulting in an electric storm.[4] This concern prompted the decision to attempt catheter ablation of VPCs triggering VF. Although several reports have described successful catheter ablation of VPCs triggering VF in some patients with structurally normal hearts, such as those with Brugada syndrome, long-QT syndrome, and idiopathic VF, successful catheter ablation of VPCs triggering VF in CPVT has not been reported. Cerrone and colleagues[5] reported that the mechanism of CPVT was due to the delayed afterdepolarization-induced triggered activity in a focal Purkinje network in a knock-in (*RyR2*) mouse. However, whether the Purkinje system is related to the mechanism of VF in CPVT or just trigger origin is still unknown.

To our knowledge, this is the first report of successful catheter ablation of the bidirectional VPCs that trigger VF, and this procedure could become one of the adjunctive

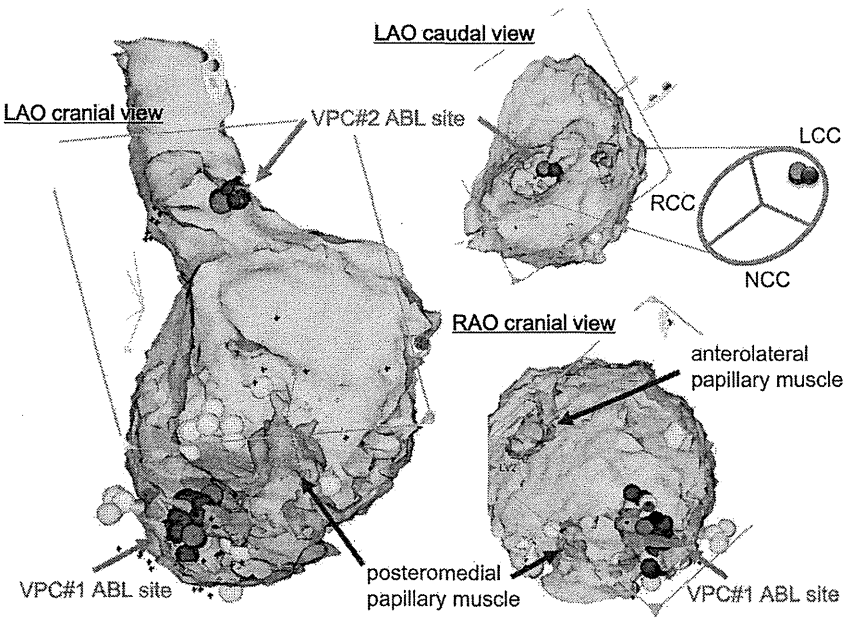

Figure 4. Electroanatomic mapping merged with contrast-enhanced CT. Red tags indicate the ABL sites. Blue tags indicate the sites with perfect pace mapping, and yellow tags indicate the sites with Purkinje potentials during sinus rhythm. The sites with perfect pace mapping and the earliest activation for VPC #1 were localized in the inferoseptal site adjacent to the base of the posteromedial papillary muscle (red arrow). Successful ablation site of VPC #2 was on the left coronary cusp (blue arrow). ABL indicates ablation; LAO, left anterior oblique; LCC, left coronary cusp; NCC, noncoronary cusp; RAO, right anterior oblique; RCC, right coronary cusp; VPC, ventricular premature contraction.

Downloaded from circep.ahajournals.org at KITAO PUBLICATIONS on February 24, 2013

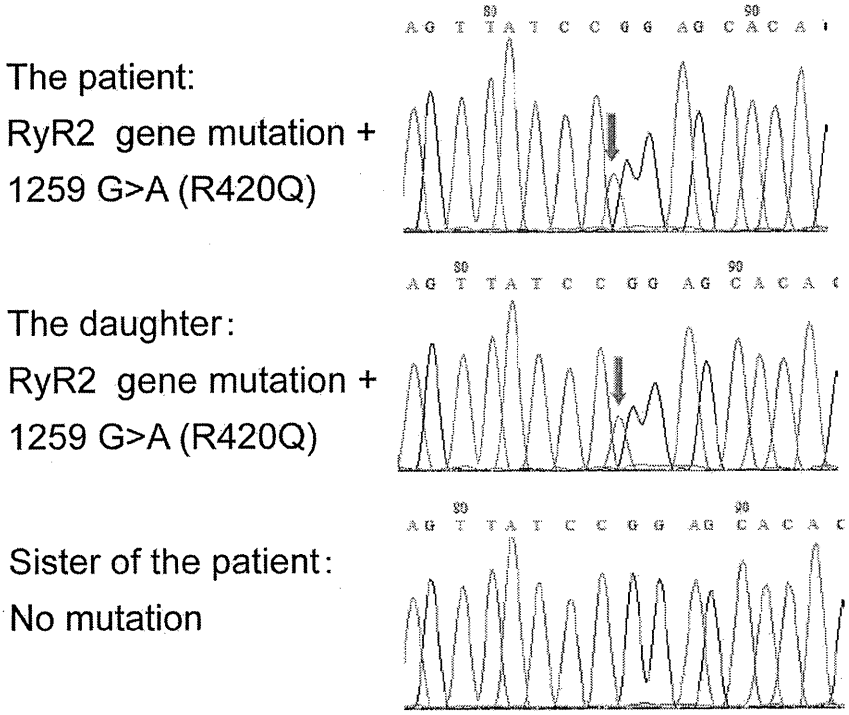

Figure 5. Results of genetic analysis. A mutation in the ryanodine receptor gene (*RyR2*) was detected in both the patient and her daughter. The mutation was not detected in the patient's sister.

therapies in patients with CPVT. To clarify the effectiveness and safety of this procedure, more cases and longer-term observation are mandatory.

Disclosures

None.

References

1. Krahn AD, Gollob M, Yee R, Gula LJ, Skanes AC, Walker BD, Klein GJ. Diagnosis of unexplained cardiac arrest: role of adrenaline and procainamide infusion. *Circulation*. 2005;112:2228–2234.
2. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, Sorrentino V, Danieli GA. Mutations in the cardiac ryanodine receptor gene (*hRyR2*) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2001;103:196–200.
3. Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, Saito A, Kurosaki K, Jouo K, Koujiro M, Konishi S, Matsuoka S, Oono T, Hayakawa S, Miura M, Ushinohama H, Shibata T, Niimura I. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart*. 2003;89:66–70.
4. Mohamed U, Gollob MH, Gow RM, Krahn AD. Sudden cardiac death despite an implantable cardioverter-defibrillator in a young female with catecholaminergic ventricular tachycardia. *Heart Rhythm*. 2006;3:1486–1489.
5. Cerrone M, Noujaim SF, Tolkacheva EG, Talkachou A, O'Connell R, Berenfeld O, Anumonwo J, Pandit SV, Vikstrom K, Napolitano C, Priori SG, Jalife J. Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia. *Circ Res*. 2007;101:1039–1048.

KEY WORDS: catecholaminergic polymorphic ventricular tachycardia ■ catheter ablation ■ arrhythmia

Downloaded from circep.ahajournals.org at KITAO PUBLICATIONS on February 24, 2013

Early Repolarization Is an Independent Predictor of Occurrences of Ventricular Fibrillation in the Very Early Phase of Acute Myocardial Infarction

Yoshihisa Naruse, MD; Hiroshi Tada, MD; Yoshie Harimura, MD; Mayu Hayashi, MD; Yuichi Noguchi, MD; Akira Sato, MD; Kentaro Yoshida, MD; Yukio Sekiguchi, MD; Kazutaka Aonuma, MD

Background—Recent evidence has linked early repolarization (ER) to idiopathic ventricular fibrillation (VF) in patients without structural heart disease. However, no studies have clarified whether or not there is an association between ER and the VF occurrences after the onset of an acute myocardial infarction (AMI).

Methods and Results—This study retrospectively included 220 consecutive patients with an AMI (57 female; mean age, 69±11 years) in whom the 12-lead ECGs before the AMI onset could be evaluated. The patients were classified on the basis of a VF occurrence within 48 hours after the AMI onset. Early repolarization was defined as an elevation of the QRS-ST junction of >0.1 mV from baseline in at least 2 inferior or lateral leads, manifested as QRS slurring or notching. Twenty-one (10%) patients had a VF occurrence within 48 hours of the AMI onset. A multivariate analysis revealed that ER (odds ratio [OR], 7.31; 95% confidence interval [CI], 2.21–24.14; $P<0.01$), a time from the onset to admission of <180 minutes (OR, 3.77; 95% CI, 1.13–12.59; $P<0.05$), and a Killip class greater than I (OR, 13.60; 95% CI, 3.43–53.99; $P<0.001$) were independent predictors of VF occurrences. As features of the ER pattern, a J-point elevation in the inferior leads, greater magnitude of the J-point elevation, notched morphology of the ER, and ER with a horizontal/descending ST segment, all were significantly associated with a VF occurrence.

Conclusions—The presence of ER increased the risk of VF occurrences within 48 hours after the AMI onset.

Clinical Trial Registration Information—http://www.umin.ac.jp; Identifier: UMIN000005533.

***(Circ Arrhythm Electrophysiol.* 2012;5:506-513.)**

Key Words: ECG ■ myocardial infarction ■ ventricular fibrillation ■ early repolarization

Early repolarization (ER), characterized by an elevation of the QRS-ST junction (J point) in leads other than V_1 to V_3 on the 12-lead ECG, has historically been regarded as an innocuous finding in healthy, young persons.[1,2] While 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) to J-point elevation (with or without ST-segment elevation).[4–8] In addition, recent evidence has linked ER to idiopathic VF in patients with no structural heart disease[9–15] and to life-threatening ventricular arrhythmias associated with chronic coronary artery disease.[16]

Clinical Perspective on p 513

Death from VF in the setting of an acute myocardial infarction (AMI) has historically been one of the most frequent causes of sudden cardiac death.[17] Prior investigators have evaluated the clinical and angiographic features and outcomes associated with VF in patients with an AMI.[18–22] In these patients, ER might be related to the VF occurrence after the AMI. However, no studies have attempted to clarify whether or not ER is associated with VF occurrences within 48 hours after the onset of an AMI. Accordingly, the purpose of this study was to clarify this point.

Methods

Study Population

Between April 2006 and August 2010, 964 consecutive Japanese patients with an AMI (239 women; mean age, 67±12 years) who underwent percutaneous coronary intervention in Tsukuba University Hospital, Tsukuba Medical Center Hospital, and Ibaraki Prefectural Central Hospital were retrospectively enrolled. Patients were eligible if they were 18 years or older and presented within 24 hours of the onset of the symptoms associated with an AMI. Every patient was asked for ECGs recorded well before the index event. Maximal

Received August 13, 2011; accepted April 9, 2012.

From the Cardiovascular Division, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki (Y.N., H.T., A.S., K.Y., Y.S., K.A.); the Cardiovascular Division, Tsukuba Medical Center Hospital, Tsukuba, Ibaraki (Y.H., Y.N.); and the Cardiovascular Division, Ibaraki Prefectural Central Hospital, Kasama, Ibaraki, Japan (M.H.).

Correspondence to Hiroshi Tada, MD, Cardiovascular Division, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. E-mail htada@md.tsukuba.ac.jp

© 2012 American Heart Association, Inc.

Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org

DOI: 10.1161/CIRCEP.111.966952

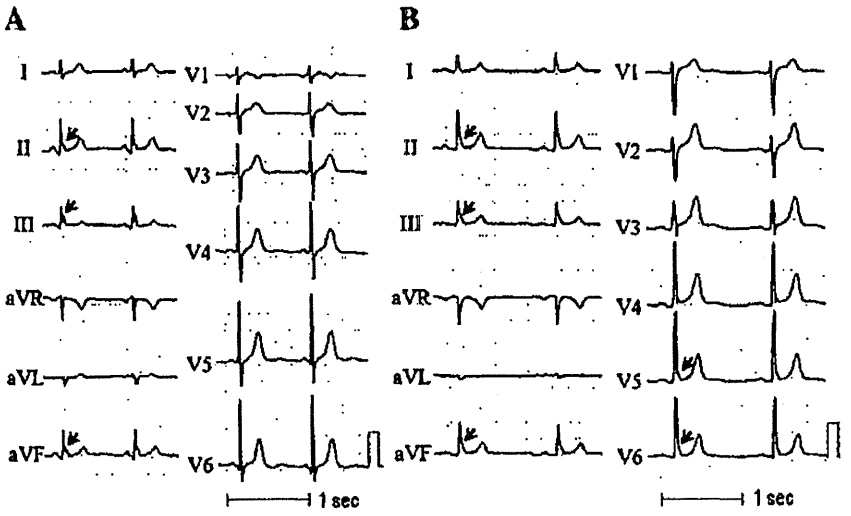

Figure 1. Baseline ECGs from patients with early repolarization. This shows 2 patients with a J-point elevation of >0.2 mV. **A**, Notched elevation (**arrows**) in the inferior leads; **B**, slurred elevation (**arrows**) in the inferior and lateral leads.

effort was taken to collect such ECGs, from which the presence of ER was evaluated. Six hundred eighty-seven patients in whom no ECGs recorded before the onset of the AMI were available were excluded from this study. Furthermore, 3 patients had a type 2 (n=2) or type 3 (n=1) Brugada ECG pattern,[23] and 31 had a QRS complex duration of ≥120 ms before the onset of the AMI. Another 23 had a prior AMI. After excluding those patients, the remaining 220 patients were finally included in this study. The mean duration from the baseline 12-lead ECG recording to the AMI onset was 5±3 months (range, 1–12).

The primary end point of this study was the occurrence of sustained VF within 48 hours after the onset of the AMI. The patients were classified based on the occurrence of sustained VF within 48 hours after the onset of the AMI. The demographic and clinical data were analyzed in both study groups. The data collection covered the age, sex, cardiovascular risk factors, culprit artery, number of diseased coronary arteries, time from the symptom onset to arrival at the emergency room, Killip class on admission, and infarct size (based on a 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 committee 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 of 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/or development of pathological Q waves on the ECG.[24] An ST-elevated myocardial infarction (STEMI) was defined as an AMI with new ST elevation at the J point in 2 contiguous 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/or ≥0.1 mV in the other leads.[24] Sustained VF was defined as that lasting >30 seconds or that requiring electric cardioversion.

ECG Analysis

To blind the ECG interpreters from the clinical characteristics and patient grouping, all tracings were scanned and coded. The early repolarization patterns were stratified according to the degree of the J-point elevation (≥0.1 mV) that was either slurred (a smooth transition from the QRS segment to the ST segment) or notched (a positive J-deflection inscribed on the S wave) in at least 2 consecutive inferior leads (II, III, and aVF), lateral leads (I, aVL, and V_4 to V_6), or both (Figure 1).[1,2,10] The J-point amplitude was measured at the QRS-ST junction in case of slurred J waves or the peak J point in the case of notched J waves, and relative to the QRS onset to minimize any baseline wandering effect.[16] We analyzed the inferior and lateral J-point elevation 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 J-point elevation from baseline. The morphological characteristics of the ER (notching or slurring) were also analyzed independently.[9,13] The anterior precordial leads (V_1 to V_3) were excluded from the analysis of the ER to avoid the inclusion of patients with right ventricular dysplasia or Brugada syndrome.[23,25] We also analyzed the ST-segment pattern after the J point independently to clarify the significance of the ST-segment characteristics according to the criteria proposed by Tikkanen[12]: An upsloping ST segment was defined as an elevation of the ST segment of ≥0.1 mV within 100 ms after the J point or a persistently elevated ST segment of ≥0.1 mV throughout the ST segment (Figure 2).[12] A horizontal/descending ST segment was defined as an elevation of the ST segment of <0.1 mV within 100 ms after the J point (Figure 3).[12] 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 without any 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 50 randomly selected patients, 1 observer evaluated a new arbitrary judgment on a separate occasion to determine the intraobserver variability.

Statistical Analysis

The continuous variables are expressed as mean±SD. The comparisons between 2 groups were tested by an unpaired t test. We used the log-transformed peak creatine kinase levels and time from the symptom onset to arrival at the emergency room, as is conventionally done. All categorical variables were presented as the number and percentage 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 univariable of the patient characteristics was compared between the VF occurrence group and no VF occurrence group, and a logistic regression analysis was performed to detect any independent significant predictors by adjusting with multivariables (reported as odds ratios [OR] with 95% confidence intervals [CIs]). The intraobserver and interobserver variability was investigated by κ statistics. All analyses were performed using the PASW 17.0 software package (SPSS, Chicago, IL). P<0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics of All AMI Patients

Among the 220 patients in whom the 12-lead ECGs before the AMI onset were obtained, 21 (10%) patients had an

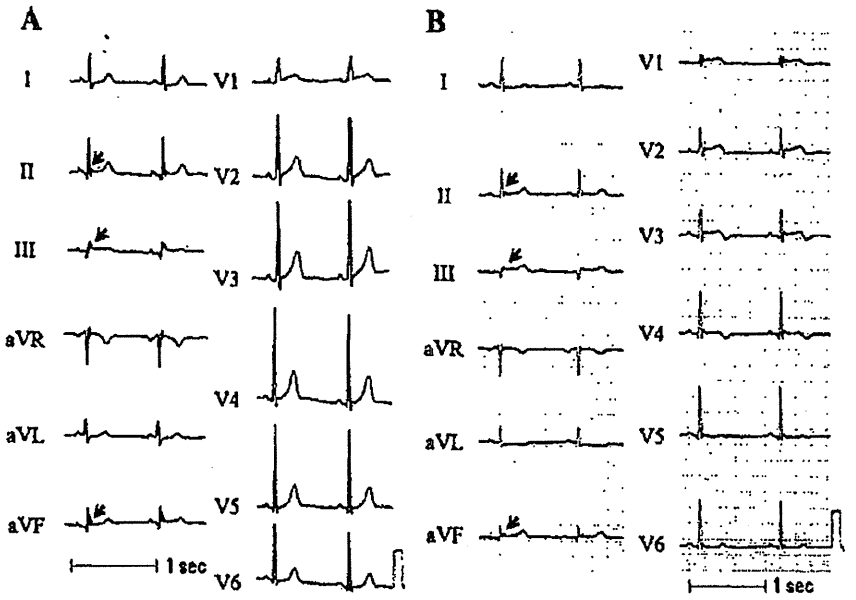

Figure 2. Representative case of preserved early repolarization. **A**, Baseline 12-lead ECG obtained 6 months before the acute myocardial infarction (AMI) onset shows a notched early repolarization with an upsloping ST segment in the inferior leads. **B**, Twelve-lead ECG during the onset of an anterior AMI showing preserved early repolarization in the inferior leads.

episode of VF within 48 hours after the onset of the AMI, and the remaining 199 (90%) did not. VF occurred before catheterization in 13 patients, during catheterization in 7, and after catheterization but within 48 hours after the onset of the AMI in the remaining patient. There was no significant difference in the age or prevalence of cardiovascular risk factors between these 2 groups (Table 1). However, the patients with VF had a greater prevalence of a male sex ($P<0.05$) and shorter duration from the symptom onset to the arrival at the emergency room ($P<0.001$) than those without (Table 1). Although the culprit artery, peak creatine kinase level, or prevalence of an STEMI did not differ between the 2 groups, the patients with VF had a greater number of diseased coronary arteries ($P<0.05$) and Killip class on admission ($P<0.001$) than those without (Table 1). Furthermore, with the analysis of the 12-lead ECG recorded before the AMI, ER was found in 10 (48%) of the patients with VF, which was more prevalent than in those without (12%; $P<0.001$; Table 1).

Predictors of VF Occurrence During an AMI

A multivariate logistic regression analysis revealed that a time from the symptom onset to the arrival at the emergency room of <180 minutes (OR, 3.77; 95% CI, 1.13–12.59; $P<0.05$), Killip class greater than I (OR, 13.60; 95% CI, 3.43–53.99; $P<0.001$), and the presence of ER (OR, 7.31; 95% CI, 2.21–24.14; $P<0.01$) were associated with the occurrence of VF within 48 hours after the onset of the AMI (Table 2). Male sex, the peak creatine kinase level, and the presence of ST-segment elevation or multivessel disease were

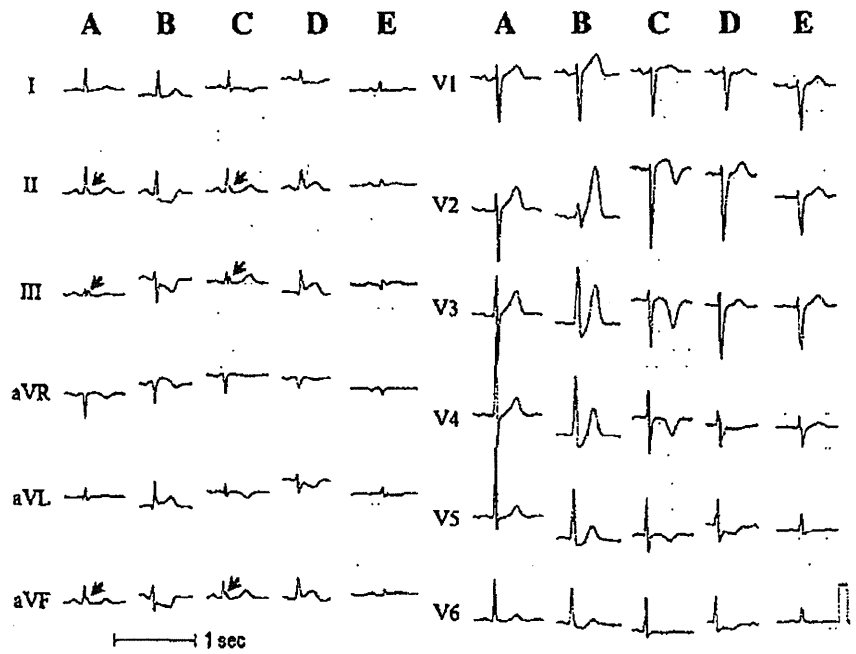

Figure 3. Representative case with serial 12-lead ECGs who consecutively had anterior and inferior acute myocardial infarction (AMI) within 3 months of each other. **A**, Baseline 12-lead ECG obtained 1 month before the AMI onset demonstrating a notched early repolarization (ER) with a horizontal/descending ST segment in the inferior leads (horizontal ST segment in leads II and aVF; descending ST segment in lead III). **B**, ECG obtained at the onset of an anterior AMI showing the lack of ER because of reciprocal ST-T changes in the inferior leads. **C**, At 2 weeks after the onset of the anterior AMI, the J point was reelevated in the inferior leads. **D**, Three months after an anterior AMI onset, the case had an inferior AMI, and the ECG at that time demonstrated no ER. **E**, The ER had still vanished 2 weeks after the inferior AMI onset.

Table 1. Demographic and Clinical Characteristics of the Patients With and Without Occurrences of Ventricular Fibrillation

	Total (n=220)	VF Occurrence (n=21)	No VF Occurrence (n=199)	*P* Value
Age, y	69±11	67±9	69±12	0.382
Male sex, n (%)	163 (74)	20 (95)	143 (72)	0.020
Cardiovascular risk factors, n (%)				
Hypertension	153 (70)	16 (76)	137 (69)	0.487
Hyperlipidemia	107 (49)	11 (52)	96 (48)	0.718
Diabetes mellitus	82 (37)	9 (43)	73 (37)	0.578
Smoking	110 (50)	12 (57)	98 (49)	0.491
Culprit artery, n (%)				0.288
RCA	73 (33)	10 (48)	63 (32)	
LAD	97 (44)	9 (43)	88 (44)	
LCx	40 (18)	1 (5)	39 (20)	
LMT	10 (5)	1 (5)	9 (5)	
Diseased coronary arteries, n	1.7±0.8	2.0±0.8	1.7±0.8	0.044
Time from the symptom onset to the ER, min	386±398	195±235	406±406	<0.001
Killip class on admission, n (%)				<0.001
I	156 (71)	6 (29)	150 (75)*	
II	32 (14)	4 (19)	28 (14)	
III	13 (6)	2 (9)	11 (6)	
IV	19 (9)	9 (43)	10 (5)*	
Peak creatine kinase levels, U/L	2315±2101	3245±2714	2193±1994	0.092
STEMI, n (%)	175 (80)	20 (95)	155 (78)	0.085
Early repolarization, n (%)	34 (16)	10 (48)	24 (12)	<0.001
Distribution				
Inferior leads	26 (12)	8 (38)	18 (9)	0.001
Amplitude				
≥0.2 mV	17 (8)	6 (29)	11 (6)	0.002
Morphology				
Notching	26 (12)	8 (38)	18 (9)	0.001
Slurring	8 (4)	2 (10)	6 (3)	0.171
ST segment				
Upsloping	9 (4)	1 (5)	8 (4)	0.602
Horizontal/descending	25 (12)	9 (43)	16 (8)	<0.001

VF indicates ventricular fibrillation; RCA, right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; ER, emergency room; and STEMI, ST-elevated myocardial infarction.

Values are reported as mean±SD or n (%).

*P<0.001 versus VF occurrence.

not associated with the occurrence of VF within 48 hours after the AMI onset (Table 2).

Detailed Characteristics of Early Repolarization for Predicting VF

Distribution

Among the 34 patients who had ER, the J-point elevation was in the inferior leads in 26 (76%) patients, in the lateral leads in 5 (15%), and in the inferior and lateral leads in the remaining 3 (9%; Table 1).

Early repolarization in the inferior leads was associated with an increased occurrence of VF before the statistical adjustment (38% versus 9%; P<0.01; Table 1) and after adjusting for multivariables (OR, 6.85; 95% CI, 2.01–23.39; P<0.01; Table 3).

Magnitude and Morphology

A J-point elevation of >0.2 mV was found in the inferior or lateral leads in 17 (8%) subjects, and the presence of a J-point elevation of >0.2 mV in the inferior or lateral leads was associated with an increased occurrence of VF (29% versus 6%; P<0.01; Table 1). A multivariate logistic regression analysis demonstrated that a J-point elevation of ≥0.2 mV in the inferior leads was an independent predictor of the

Table 2. Univariate and Multivariate Logistic Regression Analyses of Ventricular Fibrillation Occurrence

Variables	Univariate		Multivariate*	
	Odds Ratio (95% Confidence Interval)	*P* Value	Odds Ratio (95% Confidence Interval)	*P* Value
Age per year	0.983 (0.945–1.022)	0.381	0.964 (0.912–1.019)	0.198
Male sex	7.832 (1.027–59.754)	0.047	7.353 (0.663–81.538)	0.104
Time from the symptom onset to ER of <180 minutes	2.468 (0.978–6.227)	0.056	3.767 (1.127–12.587)	0.031
A Killip class greater than I	7.653 (2.815–20.807)	<0.001	13.598 (3.425–53.990)	<0.001
Peak creatine kinase levels >3000 U/L	2.495 (0.989–6.291)	0.053	0.691 (0.212–2.252)	0.540
No. of diseased coronary arteries >1	2.629 (0.980–7.052)	0.055	3.257 (0.926–11.460)	0.066
ST-elevated myocardial infarction	5.677 (0.741–43.492)	0.095	2.574 (0.223–29.695)	0.449
Hypertension	1.448 (0.508–4.130)	0.489	0.636 (0.176–2.305)	0.491
Diabetes mellitus	1.295 (0.521–3.219)	0.579	0.752 (0.231–2.454)	0.637
Smoking	1.374 (0.554–3.406)	0.493	0.937 (0.307–2.861)	0.908
Early repolarization	6.629 (2.546–17.256)	<0.001	7.305 (2.210–24.144)	0.001

ER indicates emergency room.
*All the variables in the columns were used in the multivariate model.

occurrence of VF (OR, 10.65; 95% CI, 2.35–48.34; $P<0.01$; Table 3).

The prevalence of a notched early repolarization significantly differed between the patients with VF and those without (38% versus 9%; $P<0.01$; Table 1). In contrast, the incidence of slurring did not differ between the 2 groups ($P=0.2$; Table 1). A multivariate logistic regression analysis revealed that a notched early repolarization in the inferior leads was associated with the occurrence of VF (OR, 4.88; 95% CI, 1.36–17.57; $P<0.05$; Table 3)

ST Segment

The prevalence of early repolarization with a horizontal/descending ST segment significantly differed between the patients with VF and those without VF (43% versus 8%; $P<0.001$; Table 1). Conversely, the incidence of an upsloping ST segment did not differ between these 2 groups ($P=0.6$; Table 1). A multivariate logistic regression analysis demonstrated that a J-point elevation in the inferior leads with a horizontal/descending ST segment was an independent predictor of the occurrence of VF (OR, 8.05; 95% CI, 2.18–29.70; $P<0.01$; Table 3).

Changes in the Early Repolarization Pattern Before and Just After the Onset of the AMI

Among the 34 patients who had ER in the baseline 12-lead ECG recording before the AMI, ER was still observed in the 12-lead ECG, which was recorded on admission due to the onset of an AMI in 19 (56%) patients (Figure 2). However, in the remaining 15 (44%) patients, it was not definitely confirmed on admission for an AMI (Figure 3). Conversely, among the 186 patients who had no ER in the baseline 12-lead ECG before the AMI, no patients developed any ER in the 12-lead ECG on admission.

Reproducibility of the Judgment of Early Repolarization

The intraobserver variability of the ER was $\kappa=0.93$ ($P<0.001$) and interobserver variability, $\kappa=0.87$ ($P<0.001$).

Table 3. Univariate and Multivariate Logistic Regression Analyses of Ventricular Fibrillation, According to the J-Point Pattern in the Inferior Leads*

Variables	VF, n (%)	Univariate		Multivariate*	
		Odds Ratio (95% Confidence Interval)	*P* Value	Odds Ratio (95% Confidence Interval)	*P* Value
No J-point elevation (n=186)	11 (6)	1.000		1.000	
J-point elevation of ≥0.1 mV in the inferior leads (n=26)	8 (31)	6.188 (2.265–16.908)	<0.001	6.849 (2.006–23.385)	0.002
J-point elevation of ≥0.2 mV in the inferior leads (n=14)	6 (43)	9.550 (2.929–31.135)	<0.001	10.649 (2.346–48.343)	0.002
J-point notched elevation of ≥0.1 mV in the inferior leads (n=22)	7 (32)	6.133 (2.149–17.507)	0.001	4.883 (1.357–17.565)	0.015
Inferior J-point elevation with a horizontal/descending ST segment (n=21)	8 (38)	8.805 (3.097–25.033)	<0.001	8.049 (2.181–29.696)	0.002

VF indicates ventricular fibrillation.
*The variables that were included in the multivariate analyses were the age, sex, time from symptom onset to arrival in the emergency room of <180 minutes, Killip class of greater than I, peak creatine kinase levels >3000 U/L, number of diseased coronary arteries >1, ST-elevated myocardial infarction, hypertension, diabetes mellitus, and smoking.

Discussion

Major Findings

The results of this study demonstrated for the first time the following findings: (1) approximately 15% of the AMI patients had ER in the 12-lead ECG before the AMI onset; (2) about 50% of the patients who had VF within 48 hours after the AMI onset had ER, and the presence of ER was an independent predictor for a VF occurrence within 48 hours after the AMI onset after an adjustment for multivariables; (3) as features of the ER pattern, a J-point elevation in the inferior leads, greater magnitude of the J-point elevation, notched morphology of the ER, and ER with a horizontal/descending ST segment, all were significantly associated with the occurrence of VF; (4) the ER pattern disappeared or was not well recognized in the 12-lead ECG shortly after the AMI onset in 44% of the patients who had ER; and (5) none of the patients without any ER before the AMI onset had any ER after the AMI.

Proposed Mechanism of VF in AMI Patients Who Have Early Repolarization

In the present study, in addition to an early presentation and a Killip class of greater than I, which have been reported as risk factors for VF during the early phase of an AMI,[18–22] we found for the first time that the presence of ER was a new risk factor for a VF occurrence even after an adjustment for multivariables.

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 due to a decrease in the inward sodium or calcium channel currents or 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.[26] The trigger and substrate for the development of phase 2 reentry and ventricular tachycardia/VF may eventually emerge from the transmural dispersion of the duration of the cardiac action potentials.[26]

Clinical observations suggest an association between the I_{to} density and risk of primary VF during an AMI.[26] The presence of a more prominent I_{to} in males than in females, which is thought to be causative for the predominance of ER in men,[27] may account for the 1.3 fold higher prevalence of sudden cardiac death in males than in females.[20] A much greater predominance of the I_{to} in the right ventricular epicardium than in the left ventricular epicardium[28] might also explain a higher prevalence of primary VF in patients with an acute inferior MI who have right ventricular involvement than in those without or in those with an anterior MI.[29] The loss of the right ventricular epicardial action potential dome in the ischemic region can lead to a closely coupled extrasystole through phase 2 reentry.[30,31] Thus, the fundamental mechanisms responsible for the ST-segment elevation and initiation of VF in the early phases of an AMI are considered to be similar to those in the inherited J-wave syndromes.[26,30,31] When an AMI occurs in patients who have ER, the mechanisms described above might appear more strongly than in those who do not have ER, and it might cause VF.

Characteristics of the Pattern of Early Repolarization in AMI Patients With VF

Previous studies have demonstrated the characteristics of ER in those who have had VF; a J wave was found in the inferior leads in many patients with idiopathic VF[9,11,13]; the J waves were indeed taller in the idiopathic VF group[10,13,15]; the presence of "slurring" was not useful for identifying patients with idiopathic VF[9,13] and tachyarrhythmias due to chronic coronary disease[16]; and patients with ER and a horizontal/descending ST variant had an increased hazard ratio of arrhythmic death.[12–14] In the present study, the distribution, amplitude, morphology, and ST-segment characteristics of the ER in the patients with VF in the early phase of an AMI were quite similar to those of the previous findings.[9–16] We think that the patients who have had those characteristic ER patterns are more susceptible to VF occurrence than those who have not.

Clinical Implications

Our study demonstrated that ER was an independent predictor of a VF occurrence in AMI patients and that those patients have a risk of a VF occurrence during an AMI that is 6 times greater than that in those without ER. In particular, much attention should be paid to the patients with ER in the inferior leads, a greater magnitude of the J-point elevation, a notched morphology of the ER, and an ER with a horizontal/descending ST segment in the early phase of an AMI. In those patients with ER, primary prevention of an AMI is more important than in those without.

Because of the ECG changes caused by the AMI itself, there is a high possibility that a preexisting ER might be missed with the evaluation of the ECG recorded during or shortly after the AMI onset. Therefore, the presence or absence should be assessed in an ECG that is recorded before the AMI onset. If there is no ECG available before the AMI onset on hand, a previously recorded ECG should be collected whenever possible to clarify the risk for VF.

Study Limitations

First, the approximately 10% prevalence of VF in this study appeared to be higher than that of the previous studies.[18,20,22] The prevalence of ER before the onset of an AMI was 15%, which was comparable to that in a previous study from Japan.[32] However, it was also higher than that of the previous studies in the general population of Western countries.[11] The age, sex, and race-ethnic differences between this study and the previous studies might account for the differences in the prevalence of both VF and ER.[11,18,20,22] A recent study with Japanese patients demonstrated that the incidence of in-hospital ventricular tachycardia/VF during an AMI was 13.3%,[33] which was also higher than that of the previous studies conducted in Europe and the United States.[18,20,22] Another plausible reason might be due to the adequate management of VF before catheterization. The recent spread of the use of automated external defibrillators outside the hospital and bystander cardiopulmonary resuscitation in Japan may decrease the

sudden cardiac death but increase the prevalence of VF episodes before catheterization during the acute phase of an AMI. In this study, among 13 patients who had VF episodes before catheterization, 5 patients received an appropriate shock using automated external defibrillators before arrival at the hospital, which might contribute to the high prevalence of VF in this study. Second, the small sample size limits our power and is reflected in the broad confidence intervals, most notably in the adjusted statistical analyses regarding the incidence of ER. Third, because the presence of ER was assessed with only one 12-lead ECG obtained before the AMI onset, we could not evaluate the time course and reproducibility of the ER, and the prevalence of the ER might have been underestimated.[6,10] Fourth, the information on hypokalemia, a lack of preinfarction angina, chronic kidney disease, and a family history of sudden cardiac death, which have been reported as independent predictors of VF occurrence in patients with an AMI,[18–22] were lacking in this study. Therefore, further prospective studies with a larger sample size, long-term follow-up, and the participation of many hospitals may be needed to resolve these limitations and to ensure and enhance our results.

Acknowledgments

We thank Takahito Kaji for helpful contribution to the statistical analysis.

Disclosures

None.

References

1. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. *Am J Med.* 2003;115:171–177.
2. Mehta M, Jain AC, Mehta A. Early repolarization. *Clin Cardiol.* 1999;22:59–65.
3. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. *J Electrocardiol.* 2000;33:299–309.
4. Aizawa Y, Tamura M, Chinushi M, Naitoh N, Uchiyama H, Kusano Y, Hosono H, Shibata A. Idiopathic ventricular fibrillation and bradycardia-dependent intraventricular block. *Am Heart J.* 1993;126:1473–1474.
5. Ogawa M, Kumagai K, Yamanouchi Y, Saku K. Spontaneous onset of ventricular fibrillation in Brugada syndrome with J wave and ST-segment elevation in the inferior leads. *Heart Rhythm.* 2005;2:97–99.
6. Kalla H, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant? *J Cardiovasc Electrophysiol.* 2000;11:95–98.
7. Takagi M, Aihara N, Takaki H, Taguchi A, Shimizu W, Kurita T, Suyama K, Kamakura S. Clinical characteristics of patients with spontaneous or inducible ventricular fibrillation without apparent heart disease presenting with J wave and ST segment elevation in inferior leads. *J Cardiovasc Electrophysiol.* 2000;11:844–848.
8. Tsunoda Y, Takeishi Y, Nozaki N, Kitahara T, Kubota I. Presence of intermittent J waves in multiple leads in relation to episode of atrial and ventricular fibrillation. *J Electrocardiol.* 2004;37:311–314.
9. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol.* 2008;52:1231–1238.
10. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquie JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clementy J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med.* 2008;358:2016–2023.
11. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med.* 2009;361:2529–2537.
12. Tikkanen JT, Junttila MJ, Anttonen O, Aro AL, Luttinen S, Kerola T, Sager SJ, Rissanen HA, Myerburg RJ, Reunanen A, Huikuri HV. Early repolarization: electrocardiographic phenotypes associated with favorable long-term outcome. *Circulation.* 2011;123:2666–2673.
13. Rosso R, Adler A, Halkin A, Viskin S. Risk of sudden death among young individuals with J waves and early repolarization: putting the evidence into perspective. *Heart Rhythm.* 2011;8:923–929.
14. Rosso R, Glikson E, Belhassen B, Katz A, Halkin A, Steinvil A, Viskin S. Distinguishing "benign" from "malignant early repolarization": The value of the ST-segment morphology. *Heart Rhythm.* 2012;9:225–229.
15. Miyazaki S, Shah AJ, Haïssaguerre M. Early repolarization syndrome: a new electrical disorder associated with sudden cardiac death. *Circ J.* 2010;74:2039–2044.
16. Patel RB, Ng J, Reddy V, Chokshi M, Parikh K, Subacius H, Alsheikh-Ali AA, Nguyen T, Link MS, Goldberger JJ, Ilkhanoff L, Kadish AH. Early repolarization associated with ventricular arrhythmias in patients with chronic coronary artery disease. *Circ Arrhythm Electrophysiol.* 2010;3:489–495.
17. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: structure, function, and time-dependence of risk. *Circulation.* 1992;85:I2–I10.
18. Piccini JP, Berger JS, Brown DL. Early sustained ventricular arrhythmias complicating acute myocardial infarction. *Am J Med.* 2008;121:797–804.
19. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW, Arnold AE, de Boer MJ, Gorgels AP, Michels HR, Verkerk A, Verheugt FW, Zijlstra F, Wilde AA. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation.* 2006;114:1140–1145.
20. Gheeraert PJ, De Buyzere ML, Taeymans YM, Gillebert TC, Henriques JP, De Backer G, De Bacquer D. Risk factors for primary ventricular fibrillation during acute myocardial infarction: a systematic review and meta-analysis. *Eur Heart J.* 2006;27:2499–2510.
21. Gheeraert PJ, Henriques JP, De Buyzere ML, De Pauw M, Taeymans Y, Zijlstra F. Preinfarction angina protects against out-of-hospital ventricular fibrillation in patients with acute occlusion of the left coronary artery. *J Am Coll Cardiol.* 2001;38:1369–1374.
22. Mehta RH, Starr AZ, Lopes RD, Hochman JS, Widimsky P, Pieper KS, Armstrong PW, Granger CB; APEX AMI Investigators. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. *JAMA.* 2009;301:1779–1789.
23. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. *Circulation.* 1998;97:457–460.
24. Senter S, Francis GS. A new, precise definition of acute myocardial infarction. *Cleve Clin J Med.* 2009;76:159–166.
25. Corrado D, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. *Cardiovasc Res.* 2001;50:399–408.
26. Antzelevitch C, Yan GX. J wave syndromes. *Heart Rhythm.* 2010;7:549–558.
27. Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez GJ, Scornik FS, Antzelevitch C. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. *Circulation.* 2002;106:2004–2011.
28. Peschar M, de Swart H, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. *J Am Coll Cardiol.* 2003;41:1218–1226.
29. Mehta SR, Eikelboom JW, Natarajan MK, Diaz R, Yi C, Gibbons RJ, Yusuf S. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *J Am Coll Cardiol.* 2001;37:37–43.
30. Yan GX, Joshi A, Guo D, Hlaing T, Martin J, Xu X, Kowey PR. Phase 2 reentry as a trigger to initiate ventricular fibrillation during early acute myocardial ischemia. *Circulation.* 2004;110:1036–1041.

31. Di Diego JM, Antzelevitch C. Ischemic ventricular arrhythmias: experimental models and their clinical relevance. *Heart Rhythm.* 2011;8:1963–1968.
32. Haruta D, Matsuo K, Tsuneto A, Ichimaru S, Hida A, Sera N, Imaizumi M, Nakashima E, Maemura K, Akahoshi M. Incidence and prognostic value of early repolarization pattern in the 12-lead electrocardiogram. *Circulation.* 2011;123:2931–2937.
33. Kinoshita N, Imai K, Kinjo K, Naka M. Longitudinal study of acute myocardial infarction in the southeast Osaka district from 1988 to 2002. *Circ J.* 2005;69:1170–1175.

CLINICAL PERSPECTIVE

Previous studies have reported that early repolarization (ER) was associated with idiopathic ventricular fibrillation (VF). The purpose of this study was to clarify whether or not the presence of ER in the ECG recorded before an acute myocardial infarction (AMI) onset is associated with VF occurrences in the very early phase of an AMI. In the present study, in addition to an early presentation and Killip class of greater than I, which have been reported as risk factors for VF during the early phase of an AMI, we demonstrated for the first time that the presence of ER was a new risk factor for a VF occurrence even after an adjustment for multivariables. As features of an ER pattern, a J-point elevation in the inferior leads, greater magnitude of the J-point elevation, notched morphology of the ER, and ER with a horizontal/descending ST segment, all were significantly associated with the occurrence of VF; therefore, we might recognize these patterns of ER as "malignant ER." In patients with ER, primary prevention of an AMI is more important than in those without. The ER pattern disappeared or was not well recognized in the ECG shortly after an AMI onset in 44% of the patients who had ER in the ECG recorded before an AMI onset; therefore, the presence or absence should be assessed in an ECG that was recorded before the onset of an AMI. Further prospective validation is necessary to confirm and enhance these findings.

Author's personal copy

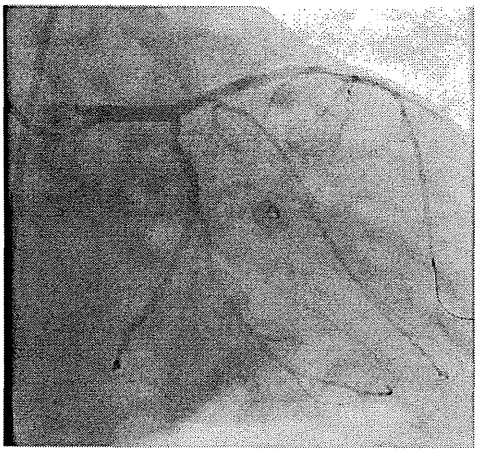

Fig. 2. Left coronary system after succesful percutanous coronary intervention.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010; 144: 1–2).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.12.032

References

[1] Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol 2006;110:7–14.
[2] Biteker M. A new classification of Kounis syndrome. Int J Cardiol Dec 3 2010;145(3):553.
[3] Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. J Am Coll Cardiol 2007;50:463–70.
[4] Chen JP, Hou D, Pendyala L, Goudevenos JA, Kounis NG. Drug-eluting stent thrombosis: the Kounis hypersensitivity-associated acute coronary syndrome revisited. JACC Cardiovasc Interv Jul 2009;2(7):583–93.
[5] Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug eluting stent. A review of available cases from the research on adverse drug events and reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81.

Electrocardiographic abnormalities and risk of complete atrioventricular block☆

Hiroshi Watanabe [a,*], Naomasa Makita [b], Naohito Tanabe [c], Toru Watanabe [d], Yoshifusa Aizawa [a]

[a] Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[b] Department of Molecular Physiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[c] Department of Health and Nutrition, University of Niigata Prefecture, Niigata, Japan
[d] Niigata Association for Comprehensive Health Promotion and Research, Niigata, Japan

ARTICLE INFO

Article history:
Received 3 December 2011
Accepted 17 December 2011
Available online 5 January 2012

Keywords:
Electrocardiography
Heart block
Conduction disease
Risk factors
Epidemiology

For more than a half-century, the benign prognosis of first-degree atrioventricular block has been repeatedly shown [1–5]. However, these studies have limitations, including the study populations (with respect to age and gender) and relatively small numbers of person-years of observation compared to low incidences of advanced atrioventricular block. A recent community-based cohort study showed that first-degree atrioventricular block is associated with the future need for pacemaker implantation and all-cause mortality [6]. Furthermore, the prolongation of QRS duration and bundle branch block have also been associated with cardiovascular events [7–9]. Here, we studied the association of common electrocardiographic findings frequently encountered in clinical practice with the risk of developing complete (third-degree) atrioventricular block in the general population.

This prospective, community-based, observational cohort study was based on annual health examinations in the Niigata prefecture, Japan [10,11]. In the prefecture, annual health examinations supported by the administration are available to adults, regardless of the presence or absence of illness. The annual examination consists of a face-to-face interview for a detailed medical history, physical examination, blood draw, chest X-ray, and 12-lead electrocardiogram. This study includes individuals who had an examination in 1993 as the baseline and ≥1 subsequent annual examination through 2005. Exclusion criteria included the presence of complete atrioventricular block or permanent pacemakers at the time of the initial examination. The diagnoses of electrocardiograms were made by physicians using the definitions based on Minnesota code. Complete atrioventricular block was diagnosed from medical history and a 12-lead electrocardiogram at a follow-up visit. Left ventricular hypertrophy was diagnosed according to the high amplitude R wave criteria [12]. Nonspecific ST-segment and/or T-wave (ST-T) abnormalities were defined as follows: (1) mild ST-T abnormality showing flat T-wave, or negative or diphasic T-wave (negative–positive type) with negative phase <1.0 mm; and (2) severe ST-T abnormality showing negative or

☆ Disclosures: None declared

* Corresponding author at: Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences, 1–754 Asahimachidori, Niigata, 951–8510, Japan. Tel.: +81 25 227 2185; fax: +81 25 227 0774.
E-mail address: hiroshi7@med.niigata-u.ac.jp (H. Watanabe).

Author's personal copy

Table 1
Baseline characteristics of study participants.

Characteristic	$n = 141,798$
Age, y	60 ± 10
Women, *n* (%)	94,872 (66.9)
Antihypertensive drug, *n* (%)	27,377 (19.3)
Heart disease, *n* (%)	3711 (2.6)
Electrocardiographic abnormalities	
First-degree atrioventricular block, *n* (%)	4053 (2.9)
Right bundle branch block, *n* (%)	2490 (1.8)
Left bundle branch block, *n* (%)	234 (0.2)
Left ventricular hypertrophy, *n* (%)	12,395 (8.7)
Atrial fibrillation, *n* (%)	1023 (0.7)
ST-T abnormality	
Mild	5742 (4.0)
Severe	564 (0.4)

Plus–minus values are means ± SD.

Table 3
Electrocardiographic abnormalities and risk of developing complete atrioventricular block in all individuals[a].

Variables	HR (95% CI)	*P* value
First-degree atrioventricular block	7.61 (4.69–12.35)	<0.001
Right bundle branch block	0.50 (0.07–3.58)	0.49
Left bundle branch block	30.08 (12.90–70.12)	<0.001
Left ventricular hypertrophy	10.07 (4.69–21.61)	0.001
Atrial fibrillation	2.25 (1.37–3.69)	<0.001
ST-T abnormality		<0.001 for trend
Mild	3.66 (2.03–6.59)	<0.001
Severe	4.52 (1.09–18.7)	0.03

[a] Models are adjusted for age, gender, body mass index, hypertension, diabetes, dyslipidemia, and heart disease. HR denotes hazard ratio; CI, confidence interval.

diphasic T-wave (negative–positive type) with negative phase ≥1.0 mm, horizontal or downward sloping ST-segment depression ≥0.5 mm, or upward sloping ST depression ≥1.0 mm. Hazard ratio (HR) and 95% confidence interval (CI) were calculated from Cox proportional-hazards models adjusted for age, gender, body mass index, hypertension, diabetes, dyslipidemia, and heart disease. A two-sided $P<0.05$ was considered statistically significant.

A total of 141,798 individuals (age, 60 ± 10 years; 94,872 women) were included in this study (Table 1). During a follow-up of 8.2 ± 4.5 years (range, 1 to 12 years), 107 individuals (0.08%) developed complete atrioventricular block, and the incidence of complete atrioventricular block was 9 per 100,000 person-years. Incidences of complete atrioventricular block in individuals with electrocardiographic abnormalities are shown in Table 2. In the multivariate models, first-degree atrioventricular block, left bundle branch block, electrocardiographic left ventricular hypertrophy, atrial fibrillation, and ST-T abnormality, but not right bundle branch block, were associated with the increased risk of developing complete atrioventricular block (Table 3). As for ST-T abnormality, there was a dose-dependent association between the severity and the risk of complete atrioventricular block (P for trend <0.001).

To study the direct effects of conduction abnormities on a risk of developing complete atrioventricular block, the analyses were repeated in 96,378 individuals who did not have structural heart disease, hypertension, antihypertensive drugs, electrocardiographic left ventricular hypertrophy, atrial fibrillation, and ST-T abnormality at baseline and did not develop interim heart disease during a follow-up. We replicated similar results to the prior analyses: first-degree atrioventricular block (HR, 15.72; 95% CI, 7.62–32.45; $P<0.001$) and left bundle branch block (HR, 74.41; CI, 22.1–250.53; $P<0.001$), but not right bundle branch block (HR, 1.41; CI, 0.19–10.33; $P=0.73$) were associated with an increased risk of developing complete atrioventricular block.

Table 2
Incidence of complete atrioventricular block with electrocardiographic covariates.

Covariates	Development of complete atrioventricular block, *n* (%)	Incidence of complete atrioventricular block/100,000 person-y (95% CI)
First-degree atrioventricular block	23 (0.57)	79 (47–111)
Right bundle branch block	1 (0.04)	5 (−5–16)
Left bundle branch block	6 (2.56)	410 (83–738)
Left ventricular hypertrophy	20 (0.16)	22 (12–31)
Atrial fibrillation	9 (0.88)	150 (52–248)
ST-T abnormality		
Mild	14 (0.24)	34 (16–51)
Severe	2 (0.35)	55 (−21–132)

CI denotes confidence interval.

This study demonstrated that first-degree atrioventricular block and left bundle branch block, but not right bundle branch block, increased the risk of developing complete atrioventricular block in a large general population, consistent with the previous studies [6–9]. Structural heart disease is one of the major causes of advanced conduction disease and there is the possibility that our results were driven by concomitant heart disease [13,14]. Furthermore, left bundle branch block causes dyssynchronous contraction of the left ventricle, possibly resulting in heart failure and the increased risk of atrioventricular block [7,15]. However, the association of first-degree atrioventricular block and left bundle branch block with the increased risk of complete atrioventricular block was significant after adjustment for heart disease and other variables, and remained significant in individuals without heart disease, suggesting that these conduction abnormalities progressed to advanced atrioventricular block.

Furthermore, we identified novel electrocardiographic risk factors for complete atrioventricular block: left ventricular hypertrophy, ST-segment abnormality, and atrial fibrillation, although the mechanisms by which these abnormalities cause atrioventricular block are unknown. Hypertrophy of the interventricular septum may cause microangiopathy and degeneration of the conduction system [16–19]. However, the frequency of complete atrioventricular block is not increased in athletes, in whom left ventricular hypertrophy is a common electrocardiographic finding, and complete atrioventricular block is very rare in patients with hypertrophic cardiomyopathy [20–23]. ST-segment abnormality may have been due to a latent myocardial disorder, while ST-segment abnormality was associated with complete atrioventricular block in individuals without heart disease. Alternatively, ST-segment abnormality may have resulted from left ventricular hypertrophy, which increased the risk of atrioventricular block in this study [24]. Very rapid impulses to conduction system during atrial fibrillation may result in developing advanced atrioventricular block. Actually, atrial fibrillation with slow ventricular response accounts for 15% to 20% of indications for pacemaker therapy [25,26].

In conclusion, we identified the electrocardiographic abnormalities that increased the risk of developing complete atrioventricular block by up to 30 times. Careful follow-up for an incident event associated with bradycardia and regular electrocardiogram recordings to detect progression of conduction disease may be important in individuals with these risk factors.

We thank Shuji Hashimoto at Fujita Health University School of Health Sciences for his assistance in statistical analysis. This work was supported by a Health and Labor Sciences Research Grant for research on measures for intractable diseases from the Ministry of Health, Labor, and Welfare of Japan (2010–145).

Author's personal copy

References

[1] Packard JM, Graettinger JS, Graybiel A. Analysis of the electrocardiograms obtained from 1000 young healthy aviators; ten year follow-up. Circulation 1954;10(3):384–400.
[2] Rose G, Baxter PJ, Reid DD, McCartney P. Prevalence and prognosis of electrocardiographic findings in middle-aged men. Br Heart J 1978;40(6):636–43.
[3] Erikssen J, Otterstad JE. Natural course of a prolonged PR interval and the relation between PR and incidence of coronary heart disease. A 7-year follow-up study of 1832 apparently healthy men aged 40–59 years. Clin Cardiol 1984;7(1):6–13.
[4] Mymin D, Mathewson FA, Tate RB, Manfreda J. The natural history of primary first-degree atrioventricular heart block. N Engl J Med 1986;315(19):1183–7.
[5] Perlman LV, Ostrander Jr LD, Keller JB, Chiang BN. An epidemiologic study of first degree atrioventricular block in Tecumseh, Michigan. Chest 1971;59(1):40–6.
[6] Cheng S, Keyes MJ, Larson MG, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA 2009;301(24):2571–7.
[7] Eriksson P, Wilhelmsen L, Rosengren A. Bundle-branch block in middle-aged men: risk of complications and death over 28 years. The Primary Prevention Study in Goteborg, Sweden. Eur Heart J 2005;26(21):2300–6.
[8] Cheng S, Larson MG, Keyes MJ, et al. Relation of QRS width in healthy persons to risk of future permanent pacemaker implantation. Am J Cardiol 2010;106(5):668–72.
[9] Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S, Froelicher VF. Prognostic significance of quantitative QRS duration. Am J Med 2006;119(7):600–6.
[10] Watanabe H, Tanabe N, Watanabe T, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. Circulation 2008;117(10):1255–60.
[11] Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J 2009;158(4):629–36.
[12] Prineas R, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. Littleton, Mass: John Wright-PSG Inc.; 1982.
[13] Harris A, Davies M, Redwood D, Leatham A, Siddons H. Aetiology of chronic heart block. A clinico-pathological correlation in 65 cases. Br Heart J 1969;31(2):206–18.
[14] Lev M. Anatomic basis for atrioventricular block. Am J Med 1964;37:742–8.
[15] Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989;79(4):845–53.
[16] Vogt M, Strauer BE. Systolic ventricular dysfunction and heart failure due to coronary microangiopathy in hypertensive heart disease. Am J Cardiol 1995;76(13):48D–53D.
[17] Strauer BE. The concept of coronary flow reserve. J Cardiovasc Pharmacol 1992;19(Suppl 5):S67–80.
[18] Panja M, Dutta AL, Kar AK, Panja S, Chhetri MK. Cardiac changes implicated in chronic heart block. J Assoc Physicians India 1991;39(9):698–701.
[19] Elizari MV, Acunzo RS, Ferreiro M. Hemiblocks revisited. Circulation 2007;115(9):1154–63.
[20] Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. N Engl J Med 1998;339(6):364–9.
[21] Corrado D, Pelliccia A, Bjornstad HH, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J 2005;26(5):516–24.
[22] Przybojewski JZ, van der Walt JJ, Ellis GC, Tiedt FA. Hypertrophic cardiomyopathy complicated by complete heart block. Case report and review of the literature. S Afr Med J 1984;66(22):847–55.
[23] Yesil M, Bayata S, Susam I, Dinckal H, Postaci N. Rare association of hypertrophic cardiomyopathy and complete atrioventricular block with prompt disappearance of outflow gradient after DDD pacing. Europace 1999;1(4):280–2.
[24] Reichek N, Devereux RB. Left ventricular hypertrophy: relationship of anatomic, echocardiographic and electrocardiographic findings. Circulation 1981;63(6):1391–8.
[25] Proclemer A, Ghidina M, Gregori D, et al. Trend of the main clinical characteristics and pacing modality in patients treated by pacemaker: data from the Italian Pacemaker Registry for the quinquennium 2003–07. Europace 2010;12(2):202–9.
[26] Samartin RC, Ferrer JM, de Carranza MJ, Mateas FR, Gonzalez JL. Spanish pacemaker registry. 6th official report of the Spanish Society of Cardiology Working Group on Cardiac Pacing (2008). Rev Esp Cardiol 2009;62(12):1450–63.

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.12.028

Hypertensive crisis: Comparison between diabetics and non-diabetics — Response to comment

Rashed Al Bannay *, Aysha Husain

Cardiology Unit, Internal Medicine Department, Salmaniya Medical Complex, Bahrain

ARTICLE INFO

Article history:
Received 5 December 2011
Accepted 17 December 2011
Available online 10 January 2012

Keywords:
Hypertensive crisis
Diabetes mellitus
Hyperglycemia

We would like to thank Professor Martin JF for his warm words and his valuable comments.

In our latest study we were not concerned differentiating true hypertensive crisis from pseudocrisis.

Patients with very high blood pressure, once they are symptomatic they don't belong to pseudocrisis category [1]. All our patients were symptomatic and been assessed through the emergency room, furthermore, absence of acute target organ involvement will prevent subjecting them to hazardous overtreatment [2].

We believe that defining hypertensive urgency where no acute target organ involvement under threat is so important. Such definition will guide the rate and urgency of blood pressure lowering, thus avoiding the anticipated morbidity of overtreatment. Even though, hypertensive urgency and hypertensive pseudocrisis are not synonymous but their common interception that acute blood pressure lowering is not indicated and in contrary it can be hazardous.

Concerning the relationship between the stress induced hyperglycemia and overall prognosis we agree with you that it can be a dismal sign.

It is so hard for a cardiologist to explain the pathophysiology of diabetes; however, a strong body of evidence suggests that patients admitted through the emergency with acute elevation of blood sugar warrant a formal GTT test as a follow up [3].

Unsurprisingly significant number of these patients will turn to be diabetics.

Furthermore, Gornik et al., recently has defined an elevated or alarming serum sugar of more than 7.8 mmol/L which is even a lower cutoff point for random hyperglycemia defined by other as 8 mmol/L [3,4].

In other words the threshold to define random hyperglycemia in the acute setting is lowered.

We agree with Chenug et al., that a major limitation of their study was the anticipation that some of their patients admitted with

* Corresponding author. Tel.: +973 39669406; fax: +973 17251303.
E-mail address: abdullarashed@yahoo.com (R. Al Bannay).

Correspondence

Response to Letter Regarding Article, "Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization"

We appreciated hearing from Casado-Arroyo et al regarding our recently published article, "Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization," showing that *SCN5A* is a novel causative gene of early repolarization syndrome.[1] In this study, we identified 3 *SCN5A* mutations in 3 unrelated patients with idiopathic ventricular fibrillation associated with early repolarization (or early repolarization syndrome). Because all of the patients had J-point elevation in the right precordial lead(s) in addition to J-point elevation in the inferior/lateral leads, Casado-Arroyo et al suggested that all of our patients have Brugada syndrome based on their recent findings that the risk of arrhythmia events is similar between patients with the Type 1 Brugada electrocardiographic pattern in 1 of the right precordial leads and patients with the Type 1 electrocardiographic pattern in >1 lead.[2] However, we respectfully disagree because our patients never met the diagnostic criteria for Brugada syndrome.[3] The diagnosis of Brugada syndrome is made when patients have a Type 1 Brugada electrocardiographic pattern, which is characterized by a prominent coved ST-segment elevation displaying a J-wave amplitude or ST-segment elevation ≥0.2 mV followed by a negative T-wave in ≥2 of the right precordial leads in the absence or presence of sodium channel blockers.[3] Although the J-point elevation was ≥0.2 mV in 1 (Patients 2 and 3) or 2 (Patient 1) of the right precordial leads in our patients, there was no clear negative T-wave such that these patients did not exhibit a Type 1 electrocardiogram. The results of a sodium channel blocker challenge are positive in almost all patients with Brugada syndrome as shown by studies performed by our group and by the Brugada group,[4,5] but the results were negative for all of our patients. Although Patient 3 had an R367H *SCN5A* mutation, which has been identified in another family affected by Brugada syndrome,[6] the penetrance is incomplete in Brugada syndrome and identical mutations in *SCN5A* can result in different phenotypes, indicating the importance of genetic modifiers and environmental influences in determining disease susceptibility.[7,8] Furthermore, the same mutation in *KCNJ8* has recently been identified in patients with Brugada syndrome and in those with early repolarization syndrome, further supporting the hypothesis.[9]

The letter by Casado-Arroyo et al presents important recent issues: the similarities and differences in both the genetic backgrounds and clinical characteristics between early repolarization syndrome and Brugada syndrome. Mutations in *SCN5A* have been identified in up to 30% of patients with Brugada syndrome,[3] and we identified *SCN5A* as 1 of the causative genes of early repolarization syndrome.[1] Furthermore, mutations in the cardiac L-type Ca^{2+} channel genes and those in *KCNJ8* have been linked to both diseases.[9–11] Because early repolarization syndrome and Brugada syndrome share genetic backgrounds, it is not surprising that both diseases also share clinical characteristics. J-point elevation is often found in the right precordial leads in patients with early repolarization syndrome, and our patients with early repolarization syndrome carrying an *SCN5A* mutation had J-point elevation in the right precordial lead(s).[1,12] In contrast, inferolateral early repolarization is found in approximately 10% of patients and is associated with an increased risk of arrhythmia events in patients with Brugada syndrome.[13] There are further similarities in the clinical characteristics, including a male preponderance, bradycardia-dependent augmentation of J-point elevation, reduction or elimination of J-point elevation during exercise, conduction abnormality, and responses to isoproterenol and quinidine.[1,5] The similarities have led Antzelevitch et al[14] to propose that both diseases represent different manifestations of a single disease termed "J wave syndromes." However, important differences also exist between the 2 diseases. The modes of initiation of ventricular fibrillation are different.[12] The early repolarization pattern is not generally associated with abnormalities in the T-wave, but the diagnostic Type 1 Brugada electrocardiogram includes a negative T-wave.[3] In the signal-averaged electrocardiogram, abnormal late potentials are frequently found in patients with Brugada syndrome but are rare in patients with early repolarization syndrome.[5] Sodium channel blockers augment ST elevation in the right precordial leads for patients with Brugada syndrome, whereas the drugs attenuate J-point elevation in patients with early repolarization syndrome.[5] Interestingly, J-point elevation was augmented and ventricular fibrillation was induced by pilsicainide in 2 of the 3 patients carrying an *SCN5A* mutation, suggesting a unique characteristic of early repolarization syndrome associated with *SCN5A* mutations.[1] Further studies are needed to elucidate the mechanism(s) responsible for the genotype–phenotype correlations of the diseases associated with J-point elevation.

Disclosures

None.

Hiroshi Watanabe, MD, PhD, FESC
Division of Cardiology
Niigata University School of Medicine
Niigata, Japan

Akihiko Nogami, MD, PhD
Division of Heart Rhythm Management
Yokohama Rosai Hospital
Yokohama, Japan

Kimie Ohkubo, MD, PhD
Division of Cardiology
Department of Medicine
Nihon University School of Medicine
Tokyo, Japan

Hiro Kawata, MD, PhD
Division of Arrhythmia & Electrophysiology
Department of Cardiovascular Medicine
National Cerebral & Cardiovascular Center
Suita, Japan

Yuka Hayashi, MD
Division of Cardiology
Niigata University School of Medicine
Niigata, Japan

Taisuke Ishikawa, DVM
Department of Molecular Pathogenesis
Medical Research Institute
Tokyo Medical & Dental University
Tokyo, Japan

Takeru Makiyama, MD, PhD
Department of Cardiovascular Medicine
Kyoto University Graduate School of Medicine
Kyoto, Japan

Satomi Nagao, MD
Nobue Yagihara, MD
Division of Cardiology
Niigata University School of Medicine
Niigata, Japan

Naofumi Takehara, MD, PhD
Yuichiro Kawamura, MD, PhD
Department of Internal Medicine
Division of Cardiovascular Respiratory & Neurology

(*Circ Arrhythm Electrophysiol.* **2012;5:e60-e61.**)
© 2012 American Heart Association, Inc.

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.112.971507**

Downloaded from circep.ahajournals.org by NAOMASA MAKITA on April 17, 2012