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% vs. 9%; p<0.01; Table 1) and after adjusting for multi-variables (OR, 6.85; 95%CI, 2.01 to 23.39; p<0.01; Table 3).

Magnitude and morphology.

A J-point elevation of more than 0.2 mV was found in the inferior or lateral leads in 17 (8%) subjects, and the presence of a J-point elevation of more than 0.2 mV in the inferior or lateral leads was associated with an increased occurrence of VF (29% vs. 6%; p<0.01; Table 1). A multivariate logistic regression analysis demonstrated that a J-point elevation of ≥ 0.2mV in the inferior leads was an independent predictor of the occurrence of VF (OR, 10.65; 95%CI, 2.35 to 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% vs. 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 to 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% vs. 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 to 29.70; p<0.01; Table 3).

8

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 prior to 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 upon admission for an AMI (Figure 3). Conversely, among the 186 patients who had no ER in the baseline 12-lead ECG prior to 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 κ=0.93 (p<0.001) and interobserver variability κ=0.87 (p<0.001).

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 developed 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 multi-variables; (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 prior to the AMI onset developed any ER after the AMI.

9

Proposed mechanism of VF in AMI patients who have early repolarization

In this 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 multi-variables.

Transmural differences in the early phases (phases 1 and 2) of the cardiac action potential,

which are created by a disproportionate amplification of the repolarizing current in the epicardial

myocardium 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-ATP}, and I_{K-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 VT/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

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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 suffering from VF

Previous studies have demonstrated the characteristics of ER in those who have suffered from 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 suffering from 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 susceptibility 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 pre-existing ER might be missed with the evaluation of the ECG recorded during or shortly after

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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 seemed 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, gender, 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 VF/tachycardia during an AMI was 13.3%,[33] which was also higher than that of the previous studies conducted in Europe and the USA.[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 (AEDs) outside the hospital and by-stander cardio-pulmonary 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 AEDs 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.

Conflict of Interest Disclosures: None.

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Table 1. Demographic and clinical characteristics of the patients with and without occurrences of ventricular fibrillation (VF).

	Total (n=220)	VF occurrence (n=21)	No VF occurrence (n=199)	*p value*
Age, years	69±11	67±9	69±12	0.382
Male gender, n (%)	163 (74%)	20 (95%)	143 (72%)	0.020
Cardiovascular risk factors				
Hypertension, n (%)	153 (70%)	16 (76%)	137 (69%)	0.487
Hyperlipidemia, n (%)	107 (49%)	11 (52%)	96 (48%)	0.718
Diabetes mellitus, n (%)	82 (37%)	9 (43%)	73 (37%)	0.578
Smoking, n (%)	110 (50%)	12 (57%)	98 (49%)	0.491
Culprit artery				
RCA, n (%)	73 (33%)	10 (48%)	63 (32%)	
LAD, n (%)	97 (44%)	9 (43%)	88 (44%)	0.288
LCx, n (%)	40 (18%)	1 (5%)	39 (20%)	
LMT, n (%)	10 (5%)	1 (5%)	9 (5%)	
Number of 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 (%)				
I	156 (71%)	6 (29%)	150 (75%)*	
II	32 (14%)	4 (19%)	28 (14%)	<0.001
III	13 (6%)	2 (9%)	11 (6%)	
IV	19 (9%)	9 (43%)	10 (5%)*	
Peak creatine kinase levels, U/L	2,315±2,101	3,245±2,714	2,193±1,994	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, n (%)	26 (12%)	8 (38%)	18 (9%)	0.001
Amplitude				
≥0.2mV	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

The values are reported as the mean±standard deviation or n (%). *p<0.001 vs. VF occurrence. ER=emergency room; LAD=left anterior descending artery; LCx=left circumflex artery; LMT=left main trunk; RCA=right coronary artery; STEMI=ST elevated myocardial infarction.

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Table 2. Univariate and multivariate logistic regression analyses of ventricular fibrillation occurrence.

Variables	Univariate Odds ratio (95% confidence interval)	p value	Multivariate* 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 gender	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 min	2.468 (0.978–6.227)	0.056	3.767 (1.127–12.587)	0.031
A Killip class > 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
Number 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=emergency room.   * All the variables in the columns were used in the multivariate model.

Table 3. Univariate and multivariate logistic regression analyses of ventricular fibrillation (VF), according to the J-point pattern in the inferior leads.*

Variables	No of VFs n (%)	Univariate Odds ratio (95% confidence interval)	p value	Multivariate* 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

*The variables that were included in the multivariate analyses were the age, sex, time from symptom onset to arrival in the emergency room of less than 180 min, Killip class of greater than I, peak creatine kinase levels greater than 3000 U/L, number of diseased coronary arteries greater than 1, ST elevated myocardial infarction, hypertension, diabetes mellitus, and smoking.
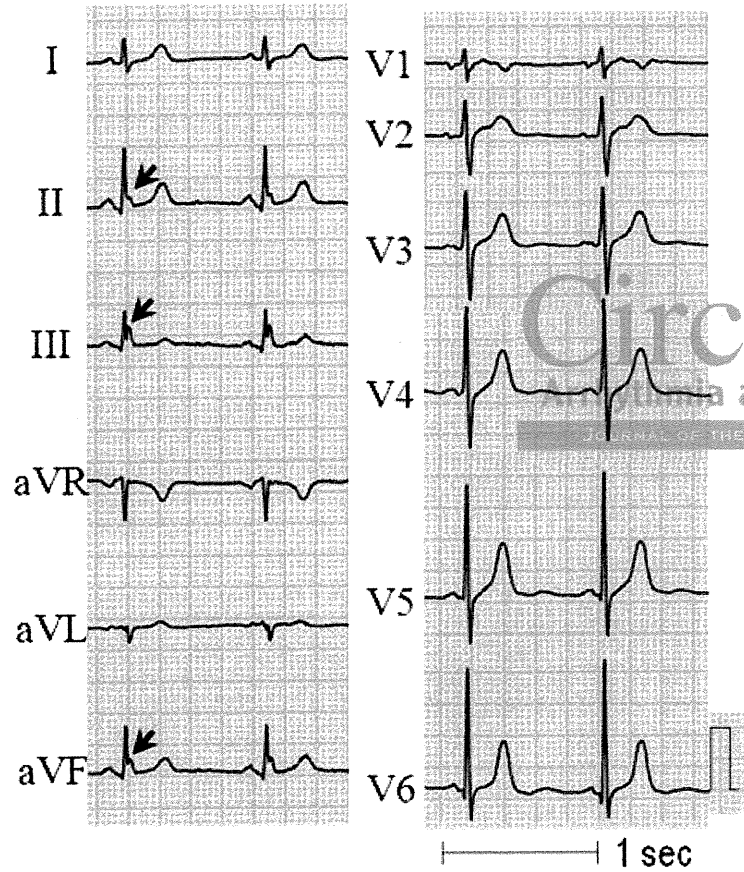
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Figure Legends:

Figure 1. Baseline electrocardiograms from patients with early repolarization. This shows two patients with a J-point elevation of more than 0.2 mV. Panel A has a notched elevation (arrows) in the inferior leads and Panel B has a slurred elevation (arrows) in the inferior and lateral leads.

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

Figure 3. A representative case with serial 12-lead ECGs who consecutively suffered from anterior and inferior AMIs within 3 months of each other. (**A**) A baseline 12-lead ECG which was 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**) An ECG which was 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 re-elevated in the inferior leads. (**D**) Three months after an anterior AMI onset, the case suffered from 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. AMI=acute myocardial infarction.

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(A)

(B)

(A)

I   V1

II   V2

III   V3

aVR   V4

aVL   V5

aVF   V6

⊢ 1 sec

(B)

I   V1

II   V2

III   V3

aVR   V4

aVL   V5

aVF   V6

⊢ 1 sec