ら静脈血採血を行い、DNA抽出キットによりDNAを抽出した。ナトリウムチャネルSCN5A遺伝子の全28エクソンをそれぞれ特異的なプライマーを用いてPCR法により増幅させ、シークエンサー（ABI310）を用いて、ダイレクトシークエンス法により、SCN5A遺伝子の全エクソンの塩基配列を決定し、データベースを基に遺伝子変異および遺伝子多型を同定した。

C. 研究結果（表2）

ブルガダ症候群と診断された19例から遺伝子解析に関する同意が得られた。19例中、1例でミスセンス変異（W1095C）が認められ、6例でSCN5Aミスセンス多型が認められた（R1193Q 4例、H558R 4例、合併2例）。

D. 考察

本研究では1症例でアミノ酸の変化を伴う（W1095C）SCN5A遺伝子のミスセンス変異（G3285T）が検出された（図1）。ブルガダ症候群に関連したチャネル機能異常を引き起こす遺伝子変異は、主に6つの膜貫通領域、ポア領域、電位センサー領域に存在することが多いのに対し、ドメイン間の変異は健常者にも認められ、チャネル機能に変化をもたらさない変異の可能性がある（Heart Rhythm. 7: 33-46, 2010）。本研究で新たに見出されたW1095C変異は第二・第三ドメイン（DII-DII）間に位置しており、チャネル機能への影響については、今後パッチクランプ法などでの検証が必要である。

SCN5AのR1193Q多型（1193アミノ酸のアルギニンからグルタミンへの変化）はブルガダ症候群やQT延長症候群、心臓伝導障害に関連すると報告されている。R1193Qによってナトリウムチャネルのピーク電流は変化しないが、持続性が延長し、不活性化が過分極側にシフトさせ、ナトリウムチャンルのloss of functionの原因となるとの報告がある（Can J Cardiol. 22 (4): 309-313, 2006）。しかし、アジア人では約10～15%の健常人にも認められる一般的な多型であり、ナトリウムチャネル機能にも影響しないという報告もある（J Med Genet. 42 e7, 2005,

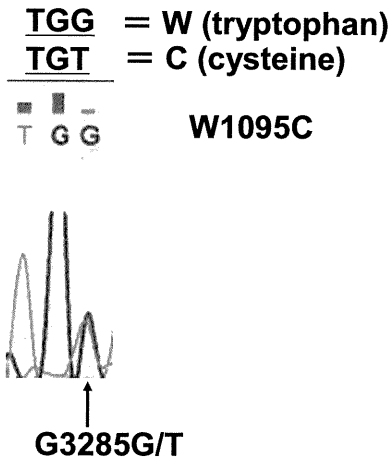

図1　ブルガダ症候群のSCN5A遺伝子ヘテロ変異（58歳男性、type 2）

表2　SCN5A遺伝子解析を行ったブルガダ症候群19例

age	gender	nucleotide chage	amino acid change	diagnosis	ECG type	VF/VT	syncope	FH	ICD	PH
39	M			Brugada	coved, I	-	-	-	-	
44	M			Brugada	saddle, II	-	-	+	+	
51	M	G3578G/A	R1193Q	Brugada	coved, I	-	+	+	+	HL
27	M	G3578G/A	R1193Q	Brugada	coved, III	VT	-	-	-	
66	M	A1673A/G, G3578G/A	H558R, R1193Q	Brugada	coved, I	-	-	+	+	OMI, HT, HL
69	M			Brugada	saddle, II	-	+	-	-	HT, HL
61	M			Brugada	saddle, II	VF	+	+	+	PAF, hypothyroidism
65	M			Brugada	coved, I	-	-	-	-	SAS, HL
70	M	A1673A/G	H558R	Brugada	saddle, II	-	+	-	-	ileus
32	M			Brugada	saddle, III	-	-	-	+	HL
40	M	A1673A/G	H558R	Brugada	coved, I	-	-	+	-	
37	M			Brugada	coved, I	-	-	+	+	SAS, depression
64	M			Brugada	saddle, II	-	+	+	+	SAS
50	M			Brugada	coved, I	VF	+	-	+	
30	M	A1673A/G, G3578G/A	H558R, R1193Q	Brugada	saddle, III	-	+	-	+	
40	M			Brugada	saddle, III	-	-	-	-	
58	M	G3285G/T	W1095C	Brugada	saddle, II	-	+	+	+	MK
50	M			Brugada	coved, I	-	+	-	+	HL
31	M			Brugada	coved, I	VF	+	-	+	

FH: familial history; ICD: Implantable Cardioverter Defibrillator; PH: past medical history; HL: hyperlipidemia (dyslipidemia); HT: hypertention; OMI: old myocardial infarction; PAF: paroxysmal atrial fibrillation; SAS: sleep apnea syndroma

Biophysics Mol Biol. 98: 120-136, 2008)。近年、ブルガダ症候群タイプ2心電図を呈し、閉塞性睡眠時無呼吸症候群と診断された症例報告があり、今後合併疾患や予後との関連性についても検討が必要である(J Electrocardiol. 42: 250-253, 2009)。

H558R はアジア人で約 10%に認められる多型である。AA 型より AG 型の方がむしろ QRS 幅が狭く、J 点が低いという心電図の特徴を呈しており、ブルガダ症候群の表現型を改善するような genetic modulator として作用するという報告がある(J Cardiovasc Electrophysiol. 20: 1137-1141, 2009)。

E. 結論

ブルガダ症候群と診断された 19 例において SCN5A 遺伝子解析を行い、1 症例で変異を、6 症例で多型を見出した。今後さらに解析を進めていくと同時に、他の遺伝子についても解析を行い、機能解析および臨床的特徴との関連性についても解析を進める必要がある。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

なし

2. 学会発表

なし

H. 知的財産権の出願・登録状況

なし

研究成果の刊行に関する一覧表

雑誌

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Naruse Y, Tada H, Harimura Y, Hayashi M, Noguchi Y, Sato A, Yoshida K, Sekiguchi Y, Aonuma K	Early repalarization is an independent predictor of occurrences of ventricular fibrillation in the very early phase of acute myocardial infarction	Circulation: Arrhythmia Electrophysiology	April 24, 2012 (E-pub ahead of print)	2012

原　著 ――――厚生労働科学技術研究 難治性疾患克服事業：心電図検診による長期にわたる疫学調査

一般住民検診におけるBrugada型心電図の長期予後調査

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Brugada症候群は右側胸部誘導におけるST上昇を特徴とし，致死性心室性不整脈による突然死をきたす可能性を有する症候群である．無症候性Brugada症候群は比較的突然死の危険性が低いと考えられているが，一般住民における長期予後に関する報告は少なく，明らかではない．われわれは，日本人の一般住民検診での循環器リスク疫学研究(Circulatory Risk of Communities Study：CIRCS)におけるBrugada型心電図の罹患率・長期予後を調査した．1983～1986年に住民検診を施行し，CIRCSに登録された40～65歳までの4，113名の健康成人(男性1,768名，女性2,345名)のうち，心疾患の既往を有する81例，および追跡調査不能の147例を除外し，3,885例を最終対象者とした．12誘導心電図を読影し，V_1～V_3誘導でJ点が0.2 mV以上の上昇とST部分がcoved型を示すものを典型的Brugada症候群(type 1)，type 2，type 3およびV_1～V_3誘導でJ点が0.1 mV以上の上昇とST部分がcoved型/saddleback型を示すものをまとめて非典型的Brugada型心電図(atypical)群，それ以外を対照(control)群と分類した．2004年までの最長22年間にわたる追跡調査を行い，24時間以内の突然死の発生をエンドポイントとした．7例(0.18%)の典型的Brugada症候群，83例(2.1%)の非典型的Brugada型心電図を認め，3,795例(97.7%)は対照群に分類された．22年間にわたる予後調査で，対照群では58例(1.5%)の突然死が認められたのに対し，典型的Brugada症候群では0例(0.0%)，非典型的Brugada型心電図群では4例(4.8%)の突然死が認められた．突然死した非典型的Brugada型心電図群のうち4症例中3症例で，下壁誘導または側壁誘導にノッチまたはスラーを認めた．V_1～V_3誘導で0.1 mV以上のJ点の上昇を有し，ST部分がcovedあるいはsaddleback型ST上昇を示す非典型的Brugada型心電図例で，突然死のリスクが高い可能性が示唆された．

Keywords
- Brugada症候群
- 突然死
- 早期再分極症候群

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Circulatory Risk in Communities Study (CIRCS)
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Ⅰ．はじめに

現在，本邦では年間約5～10万例もの心臓突然死が発生していると推定されるが，そのうち約10～20％は原因不明の突然死症候群として扱われている．Brugada症候群は右側胸部誘導におけるST上昇という特徴的な心電図所見を有し，心室細動による突然死をきたしうる症候群である[1]．アジア人男性に多く発症し，本邦における突然死症候群のなかで最も頻度が高いと考えられている．心室細動や心停止から蘇生された例，すなわち症候性Brugada症候群は高率に突然死や心室細動を再発する危険性を有し，予防的治療として植込み型除細動器(ICD)の絶対的な適応である[2]．しかし，無症候性Brugada型心電図症例は診断基準があいまいであること，一般住民における長期予後調査が十分に行われていないことから，治療・管理をどのようにすればよいのか十分に示されていない．われわれは，1969年から5地域で定期的に実施している循環器リスク疫学研究(Circulatory Risk in Communities Study : CIRCS)で得られた心電図の再解析を行うとともに，本邦の一般住民における無症候性Brugada症候群の疫学的実態を評価し，有病率・新規発症率・臨床背景・長期の自然予後を把握することを目的とした観察研究を実施した．

Ⅱ．研究対象と方法

研究対象として，筑波大学大学院人間総合科学研究科社会環境医学教室，大阪大学大学院医学系研究科公衆衛生学教室および愛媛大学大学院医学系研究科医療環境情報解析学で1969年から30年間以上継続して行われているCIRCSの登録症例を用いた．今回の研究では，1982～1986年に茨城県K町の住民健診を受診した40歳以上65歳未満の4,113名(男性1,768名，女性2,345例)のうち，心疾患の既往を有する81例，および追跡調査不能の147例を除外し3,885例を最終対象者とした．各年度の心電図を読影し，米国不整脈学会および欧州不整脈学会による2nd consensus report[1]に基づき，V_1～V_3誘導におけるJ点の0.2mV以上の上昇と上に凸型(coved型)のST上昇を認めるものを典型的Brugada症候群(type 1)と診断した．Type 2(0.2mV以上のJ点上昇および0.1mV以上のsadddleback型ST上昇を認めるもの)，type 3(0.2mV以上のJ点上昇および0.1mV未満のsadddleback型ST上昇を認めるもの)，およびJ点の0.1mV以上の上昇とcoved型あるいはsaddleback型ST上昇が認められるものをまとめて，非典型的Brugada型心電図(atypical)と分類した．J点の0.1mVを超える上昇がないものを対照(control)とした．

2004年まで22年間にわたる追跡調査を行い，転出者，死亡者を特定した．死因は死亡診断書(死亡票)，アンケート調査，救急搬送記録，診療記録などによって特定した．突然死は症状出現から24時間以内の原因不明の死と定義した．Type 1，atypical，control各群の突然死発生率を算出した．

Ⅲ．研究結果

表1に各群の背景・予後を示す．典型的Brugada症候群(type 1群)は7例(0.18%)，非典型的Brugada型心電図(atypical群)は83例(2.1%)に認められた．両群とも85％以上が男性であり，有意に年齢が高く，body mass index (BMI)が低いという特徴が認められた．

22年間の予後調査期間中の突然死発症率を，control群 3,885例中58例(1.5%)と比較したところ，type 1群7例中0例(0.0％)，atypical群83例中4例(4.8%)で，atypical群に突然死が多く認められた．

突然死を起こしたatypical群の4症例の背景を表2に，心電図を図1に呈示する．

症例1は64歳で突然死した男性で，V_2誘導で0.2mVを超えるJ点上昇と0.1mVを超えるsaddleback型ST上昇を認めたtype 2のBrugada型心電図である．aV_L誘導でスラーが，V_1誘導でノッチが認められた．

表1　対照群，典型的Brugada症候群，非典型的Brugada型心電図群の背景と突然死

	対照群 (control)	典型的Brugada症候群 (type 1)	非典型的Brugada型心電図群 (atypical)	p値
対象者数(n)	3,795	7	83	—
全対象者数における割合(%)	97.7	0.18	2.14	—
年齢(年)	54.8	57.1	58.1	0.004
性別(%, 男性)	42.4	85.7	85.5	<0.001
BMI(kg/m^2)	23.5	21.5	22.5	0.004
収縮期血圧(mmHg)	136	124	134	0.18
拡張期血圧(mmHg)	80	72	80	0.14
左室高電位(%)	15	21	16	0.91
突然死(n)	58	0	4	—
突然死発症率(%)	1.5	0.0	4.8	—

表2　突然死した4症例

	症例1	症例2	症例3	症例4
年齢·性別	64歳男性	60歳男性	63歳男性	74歳男性
J点波高(mm)	6.0	3.8	1.7	1.6
T波形	陽性	陽性	陽性	陽性
ST-T波形	saddlebach	saddlebach	saddlebach	saddlebach
ST部波高(mm)	2.0	0.8	1.4	1.2
分類	type 2	type 3	J point elevation	J point elevation
ノッチ	−	+	+	−
スラー	+	−	−	−

症例2(60歳男性)は，0.2 mVを超えるJ点上昇を有するが，ST上昇が0.1 mVを超えておらず，type 3のBrugada型心電図である．Ⅱ，Ⅲ，aV_F誘導でS波に重なるノッチが，aV_L誘導でスラーが認められた．

63歳および74歳で突然死を起こした症例3，症例4は，いずれもJ点の上昇が0.1 mV以上0.2 mV未満であり，本研究ではatypical群に分類される．症例3ではⅢ誘導にS波に重なるノッチが認められた．

Ⅳ．考　　察

今回の長期にわたる一般住民を対象とした観察研究により，以下の知見が得られた．第一に，22年間の追跡期間中，type 1群の7例で突然死は1例も認めなかった．第二に，control群と比較し，type 2·type 3を含むatypical群では突然死の頻度が高かった．第三に，atypical群のなかで突然死をきたした例では，下壁側壁誘導の早期再分極所見が多く認められた．

本研究におけるBrugada症候群の罹患率はtype 1群で0.18%であり，これまでの報告とほぼ一致していた．Brugadaらの報告[3]によると，無症候性Brugada症候群190例中，約2年(平均27ヵ月)のフォローアップで，突然死または心室細動をきたした例は8%であったのに対し，Prioriらの報告[4]では，約3年(平均33ヵ月)のフォローアップ期間内に，無症候性Brugada症候群30例中，突然死・心室細動をきたした例は1例もなかった．また本邦でも，KamakuraらのBrugada研究班は，平均48ヵ月の追跡調査にて，無症候性Brugada症候群は予後が比較的良好であったと報告[5]している．特発性心室

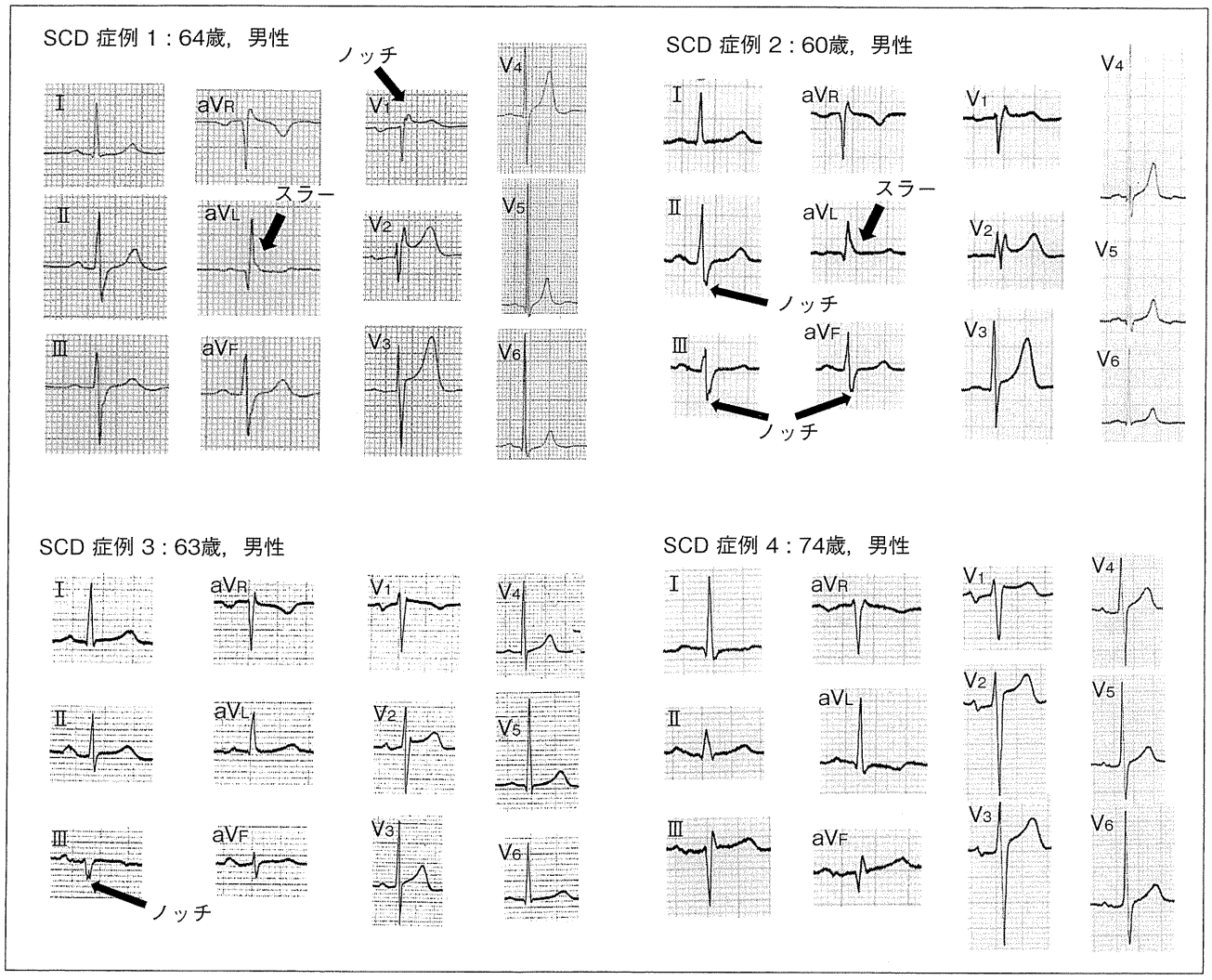

図 1　突然死した 4 症例の心電図

細動研究会(J-IVFS)の調査でも，無症候性Brugada症候群98例の平均37ヵ月のフォローアップ期間中，突然死・心室細動をきたした例はなかった[6]．今回の長期の追跡研究の結果はこれらの報告とほぼ一致しており，無症候性Brugada症候群の長期予後は比較的良好である可能性が示唆された．ただし，Brugada症候群では心電図の時間的変化が認められることが知られており，今後は心電図の経時的な解析が必要と考えられる．また，本研究ではtype 1群が7例と少なかったため，さらなる症例の蓄積が必要である．

従来，健康若年男性に多く認められる早期再分極は一般的に良性と考えられてきたが，近年，下壁誘導あるいは側壁誘導にJ点上昇を認めるいわゆる早期再分極症候群(early repolarization syndrome；J wave syndrome)が突然死と関連していることが報告[7]され注目を集めている．本研究では，これまでの報告にある下壁側壁誘導のみならず，前胸部誘導における0.1 mV以上のJ点上昇が認められた群で突然死のリスクが高い可能性が新たに示された．さらに，atypical群のなかで突然死をきたした症例では，下壁側壁誘導における早期再分極の合併頻度が高いことが示された．Kamakuraらの報告[5]では，本研究の分類同様，type 2，type 3，およびV_1～

V_3誘導における0.1～0.2 mVのJ点上昇をnon-type 1と分類しているが，non-type 1群の長期予後はtype 1群とほぼ同等，すなわち心停止・心室細動蘇生例は予後不良なのに対し，無症候性のnon-type 1群は予後が比較的良好であった．この報告のなかで，Brugada型心電図例での予後不良の予測因子として，若年の突然死の家族歴および下壁誘導での早期再分極所見の存在があげられている．本研究の結果とあわせ，type 1群でなくとも，非典型的なBrugada型心電図に下壁誘導でのJ点上昇が合併する症例で，突然死のリスクが高い可能性が強く示唆された．しかし，突然死の真の高リスク群を同定するためには，今後さらに症例を集積し，詳細な検討と長期にわたる追跡調査が必要である．

V．結　　論

約3,800例の20年以上にわたる長期予後解析の結果から，非典型的Brugada型心電図を認める例に突然死のリスクが高い可能性が示唆された．

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Early Repolarization is an Independent Predictor of Occurrences of Ventricular Fibrillation in the Very Early Phase of Acute Myocardial Infarctions

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Early Repolarization is an Independent Predictor of Occurrences of Ventricular Fibrillation in the Very Early Phase of Acute Myocardial Infarctions

Running title: *Naruse et al.; Early repolarization and VF during an AMI*

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Abstract:

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 electrocardiographic 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 based on 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 experienced 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 less than 180 minutes (OR=3.77; 95% CI=1.13–12.59; $p<0.05$), and a Killip class of 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.

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 V1 through V3 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]

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 those 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 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 msec before the onset of the AMI. Another 23 experienced 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 endpoint 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, gender, 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 pathologic 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 two contiguous leads

with the following cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in the other leads.[24] Sustained VF was defined as that lasting longer than 30 seconds or that requiring electrical 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 V4 to V6), 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 in order 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 two 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 morphologic characteristics of the ER (notching or slurring) were also analyzed independently.[9,13] The anterior precordial leads (V1 to V3) were excluded from the analysis of the ER in order 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 msec 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, one observer evaluated a new arbitrary judgment on a separate occasion to determine the intraobserver variability.

Statistical analysis

The continuous variables were expressed as the 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 percent in each group and were compared by a chi-square analysis or Fisher's exact test. An overall chi-square test for a 2 x 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 multi-variables (reported as odds ratios [OR] with 95% confidence intervals [95% CIs]). The intraobserver and interobserver variability was investigated by Kappa statistics. A p value <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 prior to the AMI onset were obtained, 21

(10%) patients experienced an 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 gender ($p<0.05$) 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 less than 180 minutes (OR, 3.77; 95%CI, 1.13 to 12.59; $p<0.05$), Killip class greater than I (OR, 13.60; 95%CI, 3.43 to 53.99; $p<0.001$), and the presence of ER (OR, 7.31; 95%CI, 2.21 to 24.14; $p<0.01$) were associated with the occurrence of VF within 48 hours after the onset of the AMI (Table 2). A male gender, the peak creatine kinase level, and the presence of ST-segment elevation or multi-vessel disease were 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% 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 $\geq$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).

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.

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}, $I_{K\text{-}ATP}$, 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 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

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