図9
Brugada 症候群モデルでの伝導遅延と ST 上昇の形態
心外膜面 (Epi) 活動電位は spike and dome を示し，伝導遅延がない状態でも J-ST 上昇，陰性 T 波がみられる．さらに，心外膜面の伝導遅延が増強すると，J-ST 上昇，陰性 T 波の増大がみられた．
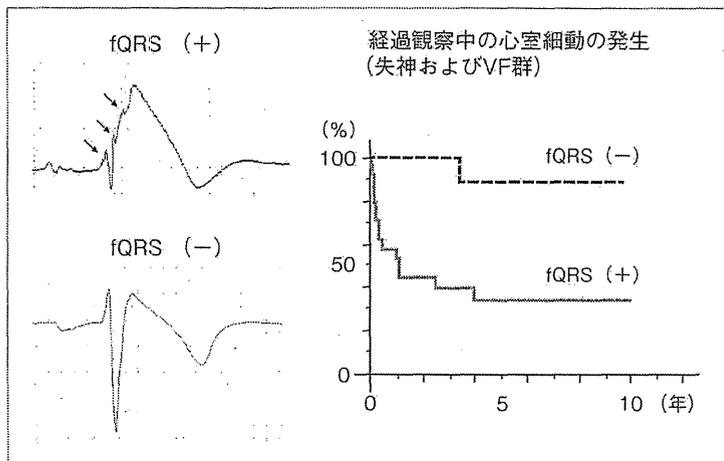〔文献 22) より引用改変〕

図10
Brugada 症候群と fragmented QRS
矢印は QRS 内の多棘性 R 波を示す．fQRS 陽性例では心室細動発生が多い．
〔文献 44) より引用改変〕

registry）では，308 例の心停止を有さない Bruga-da 患者で，fQRS は症状（失神），心室不応期の短縮（＜200 msec）とともに不整脈発生の独立した予測因子であることが示された[50]．

6．Brugada 症候群での脱分極異常・再分極異常とリスク評価

　Brugada 症候群では様々なリスク評価のための指標が報告されているが，本邦で多くみられる検診で発見された無症候例にそれらの指標をあてはめた場合，十分な感度，特異度を有しているとはいいがたい．たとえば，ほとんどの大規模研究で予後予測因子とされる type 1 心電図[50,51]は，Kamakura らの日本人を対象とした多施設共同研究で予測因子とならず，VF の既往，突然死家族歴，下側壁誘導の早期再分極が日本人でのリスクであることが示されている[4]．これは本邦では検診で発見された例を対象とすることが多いためである．症状がなく濃厚な家族歴を有さないなどの特徴を有し，無症候例の新規発

症率がそれほど高くないことなどが影響していると思われる.

リスク評価に有用な指標を明らかにするため, 自検例の Brugada 症候群患者 293 例 (無症状 196 例, 失神 81 例, VF 16 例) で症状, 年齢, 性別, 安静時心電図指標, プログラム刺激の誘発性, 加算平均心電図, ピルシカイニド負荷と経過観察中のイベント発生について検討した. 多変量解析では症状 (失神, VF 既往, HR 10.6), fQRS (HR 6.5), 下側壁誘導早期再分極 (HR 2.2), ST レベル自然変動 (≧0.2 mV) (HR 15.2) が独立した予後予測因子であった. 全体の心事故発生率をみると, 多変量解析で予測因子とした指標を多く有している症例ほど, 心事故の早期発症がみられた. 無症候例に限ると, 上記項目が 0 ないし 1 項目のみの例ではほとんどイベントがみられないのに対し, 2 項目以上有するものでは 10 年程度の経過で約 3 割の症例に VF の新規発症がみられた. 多項目を有するほど予後不良な傾向は失神例, VF 例でも同様で, リスク項目を多く有する例に対しては ICD の早期・頻回作動を防ぐためにキニジンなどの抗不整脈薬併用も考慮すべきである. この検討で得られたリスク評価となる心電図指標は脱分極異常 (fQRS), 再分極異常 (ST 変動, 早期再分極) を含んでおり, 両者が併存する例ほど VF 発生のリスクが高まると考えられる.

早期再分極・J 波と関連した特発性 VF および Brugada 症候群について概説したが, 特発性 VF は症例の概念が報告されてからまだ日が浅い. 今後, 様々な知見が報告されることになるであろう. しかしながら発生頻度は極めて少ないため, 検診例などで遭遇する早期再分極例にいたずらな不安を与えることは避けなければならない. Brugada 症候群は最初の報告から約 20 年が経過し, 様々な知見が得られたが, 無症候例でのリスク評価においては臨床的に感度・特異度の高い有用な方法が開発されることが望まれる.

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早期再分極とJ波症候群
—細胞学的成因について

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はじめに

　健常人でしばしばQRS後のST部が1〜2mm以上の上昇を示すことがあり，早期再分極（early repolarization syndrome；ERS）と呼ばれ，健常な若年者や運動家，黒人に多く，病的意義には乏しい所見と考えられていた．ERSと不整脈の関連としては，1992年にBrugadaなどが心室細動例で右側胸部誘導でのST上昇を有する例を報告し，現在ではBrugada症候群として広く知られている．心室細動と右側胸部誘導以外のJ波・ERSの関連性は，Aizawaらが1993年に報告した特発性心室細動例で，下壁誘導のJ波の増大と心室細動発生が関連することを示した．さらに，2008年にHaïssaguerreらがBrugada型波形を示さない特発性心室細動例の31％にERSを伴うことを報告した．2010年には，Antzelevitchらがこれらの特発性心室細動をJ波症候群として1つの疾患概念としてまとめ，Brugada症候群もその1型であるとしている[1]．

J波，ERS波形の機序

　ERSでは，しばしばJ点よりST部になだらかに移行するQRS終末部（スラー）やQRS終末部のノッチの後にこぶ型の波（J波）を伴う．一般的なERSの心電図学的な特徴は，J点でのノッチ，スラーの存在，凹型のST上昇，ERSを示す誘導での陽性T波で，経過中にしばしばT波高の増減を認める．通常V$_{2\sim4}$ないしV$_5$付近に多くみられ，aV$_R$誘導では鏡像的ST低下がみられる．また，QT間隔は短縮傾向を示す．

　特発性心室細動と関連するERSでは，特にJ点の波高が0.2mV以上，著明なJ波，下壁誘導ないし下側壁誘導でのERS，QT短縮，ST部分が水平型ないし下降型を示すことが多いとされている．このERSでは下側壁誘導での変化が主であり，左室心筋の異常を反映すると考えられる．

　J波およびERSの機序としては，Yanらによりイヌ心筋切片を用いた活動電位記録・貫壁性心電図記録で詳細に調べ，活動電位第1相ノッチがJ波形成に関与することを報告している[3]．

　左室，右室心筋とも，心内膜側，心筋中層，心外膜側心筋でイオンチャネルの分布や自律神経の影響の違いにより，活動電位波形に異なりがみられる．特に脱分極直後の再分極早期では一過性外向きカリウム（K）チャネルによる外向き電流（I$_{to}$）が再分極の初期に活性化し，再分極早期の活動電位の変化をもたらす．ナトリウムチャネルの活性化により脱分極した心筋細胞（活動電位第0相）は，再分極早期にI$_{to}$により再分極側に電位が引き戻される（活動電位第1相）．引き続き電位依存性の外向きK電流（I$_{Ks}$，I$_{Kr}$）の活性化と内向きのカルシウム（Ca）電流（I$_{Ca-L}$）の活性化のバランスにより，活動電位の第2相のプラトー相から第3相が形作られる．第3相付近より静止膜電位を保持する内向き整流性K電流（I$_{K1}$）の活性化により，さらに再分極が進行し，静止膜電位に復帰する（第4相）（図1）[2]．心筋各層での活動電位波形の違いは，さまざまな時相で心内膜−心外膜間に電位差を生じる原因となり，通常，心外膜側から心内膜側へ向かう電位差は心電図で陰性波を形成し，心内膜側から心外膜側へ向かう電位差は心電図で陽性波を形作る．
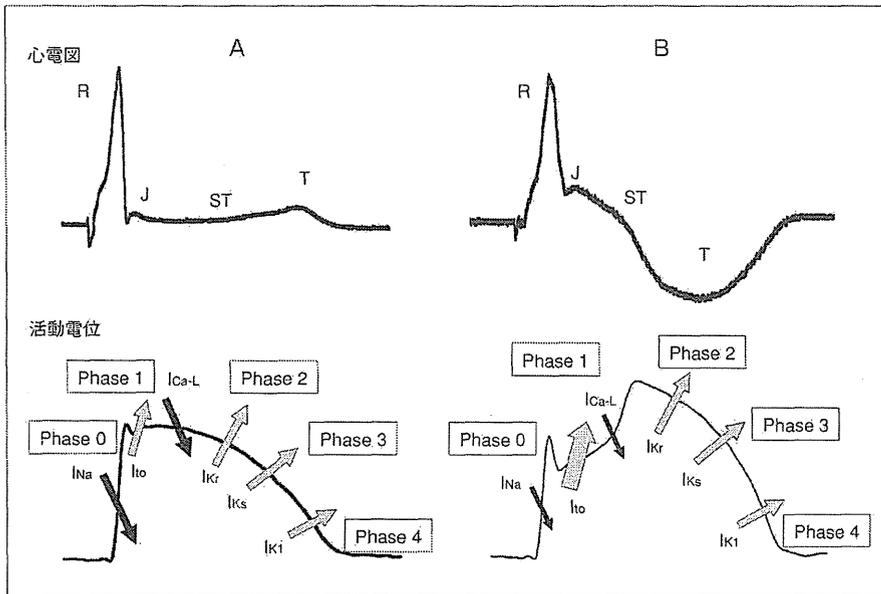
図1
活動電位と各時相でのイオン電流
の流れ
A：正常波形；活動電位第0相から3
　相にかけ，順次ナトリウム電流
　(I_{Na})，一過性外向き電流(I_{to})，内
　向きCa電流(I_{Ca-L})，外向きの遅延
　整流性K電流(I_{Kr}, I_{Ks})，内向き整
　流性K電流(I_{K1})の活性化が起こり，
　活動電位を形成する．
B：J波症候群・Brugada症候群；第
　1相ノッチの増大によりJ-ST上昇
　が発生する．
（文献2より改変引用）

　この活動電位のサイクルの中でI_{to}が非常に大きいと，活動電位第1相で深いノッチが形成されるようになる．このI_{to}を増大させる要因としては，イオンチャネルの遺伝子変異や，自律神経バランスの変化，加齢，体温変化，薬剤などによる内向き電流の減少ないし外向き電流の増大があげられる．第1相ノッチは心外膜側心筋で著明で，心内膜側心筋では小さいため，この時相で心内膜から心外膜側への電位差を生じ，心電図ではQRS終末部のスラーないしJ波を形成する[3]．この活動電位第1相のノッチは体温，心拍数，自律神経活性などで，J波の臨床的な変化と一致した変動を示す．第1相ノッチ形成に重要なI_{to}は心内膜側よりも心外膜側に，左室よりも右室に，心尖部よりも流出路などの心基部に多く存在するため，動物モデルでは右室心筋の心電図で大きなJ波がみられる（図2）．正常の興奮伝播では心内膜面より心外膜側へ興奮が進み，心外膜面は脱分極が心筋層内で最も遅く開始されるため，活動電位第1相ノッチがQRS終末部に位置し，スラーやJ波として反映される．低体温や抗不整脈薬などにより心外膜側心筋への興奮伝播が遅れると，第1相ノッチの増大と相まって顕著なJ波が出現する．

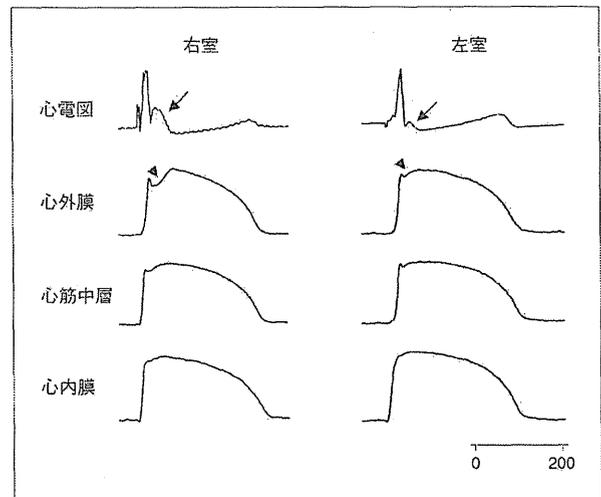図2　心室，心筋層内での活動電位の異なり
　イヌ灌流心筋切片で記録した活動電位と心電図．心外膜側では第1相ノッチが大きく（矢頭），心電図でJ波（矢印）が記録される．いずれも右室心筋で著明である．

　J波に引き続くST上昇は活動電位第2相での心外膜-心内膜間の電位差で説明される[4]．第2相では再分極はなだらかに進行するが，第1相でノッチを形成した心外膜側心筋の活動電位は，心内膜側よりも深い電位のまま第2相を形成し，心外膜面から心内
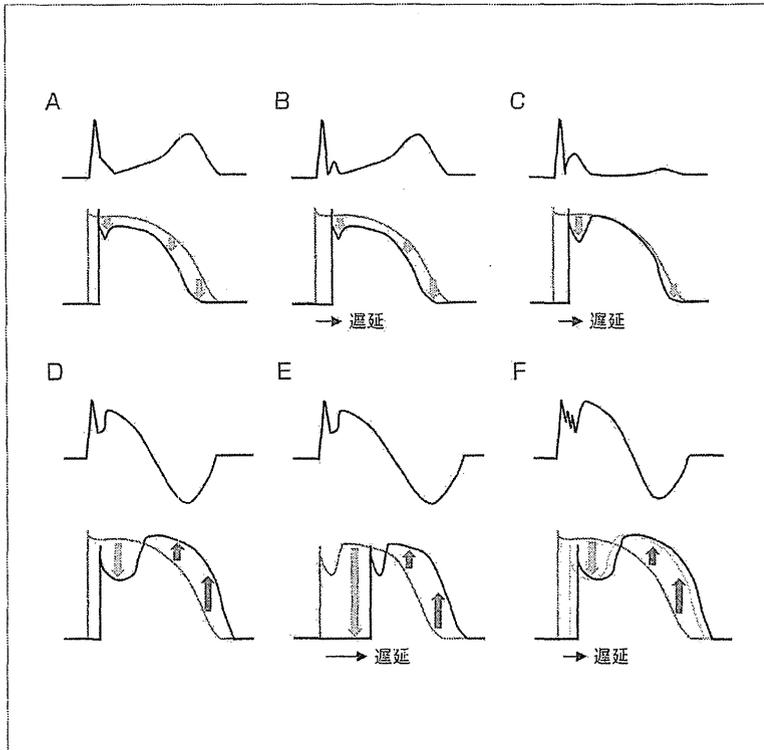
図3 ERS，Brugada症候群の心電図の形成
A：早期再分極（スラー）；心外膜側心筋活動電位のノッチと，再分極相での電位差がスラーとST上昇をきたす.
B：早期再分極（J波）；心外膜側心筋の興奮伝播が遅れると，第1相ノッチのタイミングも遅れ，心電図でJ波を形成する.
C：早期再分極（J波＋水平型ST）；活動電位ノッチ増大は引き続く第2相ドームと活動電位長を変化させ，J波増大と水平型ST部分を形成する.
D：BrS波形（再分極異常）；再分極異常によるBrugada症候群波形．心外膜面での第1相ノッチ増大と活動電位延長がST上昇と陰性T波を形成する.
E：BrS波形（脱分極異常）；脱分極異常によるBrugada症候群波形の説明．RVOT局所の伝導遅延によりほかの右室部位との電位差を生じ，Brugada波形となる.
F：BrS波形（再分極異常＋脱分極異常）；再分極異常と脱分極異常の混在によるBrugada波形．再分極異常によりST上昇が出現し，局所の伝導遅延によりさらに波形が増強される．実線（黒）は心外膜側心筋の電位を示す．実線（灰色）は心内膜側心筋（A〜D，F），右室のほかの部位（E）を示す．Fの灰白色実線は心外膜側での伝導のばらつきを示す.

膜側への電位差を生じ，基線より上方に変位したST部分を形成する．第3相での内膜−外膜間の電位差と急峻な活動電位の終末はT波を形成する．J波症候群ないしERSではJ波に引き続くST部分が水平型ないし下降型を示すものはハイリスクと考えられている．これは活動電位第1相ノッチがさらに増大すると，第2相での大きな活動電位ドームを形成する原因となり，この結果，第2相から3相にかけて心内膜面と心外膜面の活動電位の電位差が小さくなるため，ST部分の波形が水平型ないし下降型を示すようになる（図3）.

◎ Brugada型心電図の機序

　Brugada症候群での心電図はconsensus reportにより3型に分類される．J点でのST上昇が2mm以上でcoved型のST上昇と陰性Tを伴う波形はタイプ1心電図といわれる．J点で2mmを超えるsaddle back型ST上昇（ST部分は1mm以上）で陽性T波を伴う

ものはタイプ2，タイプ3はST上昇が1mm未満のcoved型ないしsaddle back型のものと定義される.

　動物モデルによるBrugada症候群の機序は，左室のJ波の機序と同様に説明される[4]．Brugada症候群は右室流出路（right ventricular outflow tract；RVOT）を中心とした不整脈基盤が存在するため，Brugadaモデルでは右室心筋を使用し，臨床的病態が説明されてきた．右室心筋では心外膜側でI_{to}が豊富なため，活動電位第1相のノッチが非常に大きく，内膜側との間で大きな電位差を形成（心外膜＜心内膜）するため，左室心筋のJ波−ERSよりも著明なBrugada型ST上昇を引き起こす（図4）．また，第1相ノッチの増大による再分極の促進は内向きCa電流の活性化を遅延させ，プラトー相でのCa電流の増加により活動電位ドームの増大および活動電位長の延長を招く（spike-and-dome型活動電位）．活動電位ドームの増大と活動電位長延長による第2〜3相にかけての心外膜より内膜側への電位差（心外膜＞心内膜）は，深い陰性
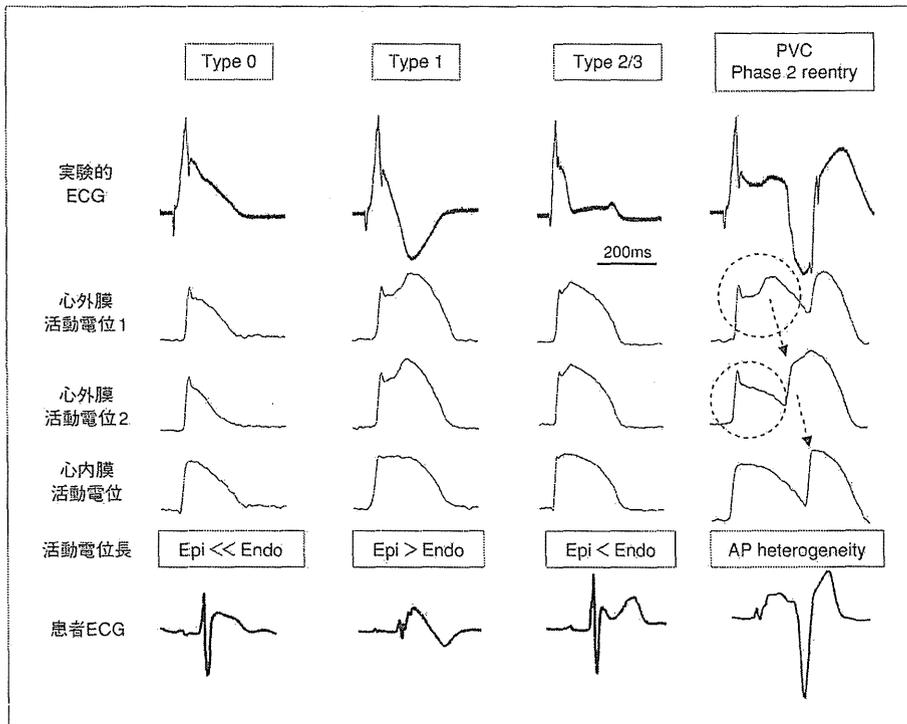
図4
Brugada症候群モデルにおける
活動電位変化
主に心外膜面の活動電位の変化により心電図波形が変化する．心外膜側心筋でspike-and-dome型とloss-of-dome型活動電位が同時に存在する（破線円）と，その電位差からphase 2 reentryが発生する．詳細は本文参照．

（文献6より改変引用）

T波を生じる（図4）[5]．

　右室心外膜側心筋の活動電位はさらにダイナミックに変化する．I_{to}の電流増加により第1相ノッチがさらに深くなると，電位依存性Ca電流が十分に活性化されなくなり，第2相ドームが形成されず，急激な活動電位の短縮が起こる（loss-of-dome型活動電位）（図4）．心内膜側活動電位の変化は小さいため，活動電位再分極相の全相にわたり心内膜より心外膜側へ向かう電位差を生じ，心電図では著明なST上昇と，陰性T波の消失が起こる[6]．この陰性T波が消失した波形は心室細動と関連してみられることが多い．

　一方，I_{to}活性化がそれほど強くなく，第1相ノッチが比較的小さいと，活動電位長は心外膜面よりも心内膜面で長い正常パターンとなるため，J波と心電図終末部の陽性T波を生じ，タイプ2ないし3心電図となる．

　J波症候群ではBrugada症候群ほど著明なST上昇，陰性T波がみられることは少ないが，J波症候群は左室を中心とした不整脈基盤が存在すると考えられ，ST

上昇がBurgda症候群ほど強くならないことや，ST上昇が不整脈発生前などに一過性に起こるためにとらえられていない可能性，活動電位が変化する心外膜面の部位が狭く，体表面心電図に反映されていない可能性があげられる．

伝導障害とJ-ST上昇

　J波症候群やBrugada症候群では伝導障害の所見が多く，この伝導障害自体がST上昇を引き起こすとの考え方もある．臨床的に両症候群とも，しばしば加算平均心電図による遅延電位が陽性となり，特にBrugada症候群では，QRS幅の増大やQRS内の多棘性スパイクなどの伝導障害の所見が予後と関連することも報告されている．最近ではNademaneeらがBrugada症候群で心外膜側アブレーションを行い，RVOTで低電位，遅延電位が記録されることを報告している[7]．伝導障害説ではBrugada症候群のRVOTで伝導遅延が存在し，右室のほかの部位に比べ著明に興奮伝播が遅延するため，QRS直後でRVOTに向かう電

位差が生じ，ST上昇が起こるとされる（図3）．また，RVOTが遅れて興奮した時相では，右室のほかの部位の興奮はすでに終了しており，ST部分後半部でRVOTからほかの部位に向けて電位勾配が生じ，陰性T波が形成される．J波症候群でも，心室中隔や左室自由壁の伝導遅延による局所的な興奮伝播の遅延がJ波を形成すると説明することも可能である．

伝導障害説では心筋障害による著明な伝導遅延がRVOTに存在し，心拍数や自律神経変動などに伴いSTレベルが著明に変動することに関しては説明が困難である．また，活動電位で大きな第1相ノッチを有する部位の興奮が遅延すると，局所再分極の進行も遅れるため，J-ST上昇と陰性T波の増強がみられることからも[5]，再分極異常と脱分極異常は相容れないものではない．

不整脈の発生

J波症候群もBrugada症候群も，不整脈発生は心外膜面の活動電位のばらつきから発生する機能的リエントリー（phase 2 reentry）がトリガーとなっていると考えられている[4]．Brugada症候群ではST上昇が発作前に増強することが多く，心外膜側活動電位の第1相ノッチが急激に増大する状況と考えられる．心外膜側心筋での活動電位波形の急激な変化は心外膜面で一様に起こらず，部位による活動電位および不応期のばらつきを引き起こし，活動電位長の長いspike-and-dome型と短いloss-of-dome型の活動電位が混在をもたらす．この結果，活動電位後半部で心外膜面に大きな電位差が発生し，loss-of-dome型活動電位の部位が電位差により脱分極するため，新たな興奮が発生する．さらに，心筋内の不応期のばらつきに応じて，機能的リエントリーにより多形性心室頻拍を発生する[5]．Aibaらは動物モデルを用い，伝導障害が存在すると，phase 2 reentryで発生した心室頻拍の興奮前面が分裂し細動に移行することも示しており，再分極異常が心室性不整脈発生のトリガーで，伝導障害が心室細動への移行・持続を引き起こす基質にな

ると考えられる[8]．伝導障害を主体とする説では障害心筋の遅延伝導そのものや，伝導遅延により遅れた部位の電位差により，心室頻拍の発生が説明される．

おわりに

J波症候群，Brugada症候群では心外膜側心筋の活動電位の再分極異常説が，臨床病態を説明するのに非常に有用であるが，臨床的には脱分極異常を示す所見も多く，脱分極異常を主体に病態を説明する説も根強い．イオンチャネルの遺伝子異常が存在すると，加齢により心筋障害を引き起こすことも知られており，また，心筋障害そのものも活動電位変化を起こすことから，実際の病態としては再分極異常，脱分極異常の両者が密接に関連して心室性不整脈を引き起こす原因となっていると考えられる．

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Identification of high-risk syncope related to ventricular fibrillation in patients with Brugada syndrome

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BACKGROUND Syncope in patients with Brugada syndrome is usually associated with ventricular tachyarrhythmia, but some episodes of syncope can be related to autonomic disorders.

OBJECTIVE The purpose of this study was to investigate the characteristics of syncope to differentiate high-risk syncope episodes from low-risk events in patients with Brugada syndrome.

METHODS We studied 84 patients with type 1 electrocardiogram and syncope. Patients were divided into 2 groups: patients with prodrome (prodromal group; n = 41) and patients without prodrome (nonprodromal group; n = 43).

RESULTS Ventricular fibrillation (VF) was documented at index event in 19 patients: 4 patients (21%) with documented VF experienced a prodrome prior to the onset of VF, whereas 15 patients (79%) did not have symptoms prior to documented VF (*P* <.01). Twenty-seven patients in the prodromal group and 7 patients in the nonprodromal group were considered to have syncope related to autonomic dysfunction. Syncope in other patients was defined as unexplained syncope. During the follow-up period (48 ± 48 months), recurrent syncope due to VF occurred in 13 patients

among patients with only unexplained syncope and was more frequent in the nonprodromal group (n = 10) than in the prodromal group (n = 3; *P* = .044). In multivariate analysis, blurred vision (hazard ratio [HR] 0.20) and abnormal respiration (HR 2.18) and fragmented QRS (HR 2.39) were independently associated with the occurrence of VF.

CONCLUSION Syncope with prodrome, especially blurred vision, suggests a benign etiology of syncope in patients with Brugada syndrome.

KEYWORDS Brugada syndrome; Neurally mediated syncope; Prodrome; Syncope; Ventricular fibrillation

ABBREVIATIONS BS = Brugada syndrome; ECG = electrocardiogram; f-QRS = fragmented QRS; HUT = head-up tilt; ICD = implantable cardioverter-defibrillator; NMS = neurally mediated syncope; OH = orthostatic hypotension; VF = ventricular fibrillation

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Introduction

Syncopal episodes in patients with Brugada syndrome (BS) are usually associated with the occurrence of ventricular tachyarrhythmias. Spontaneous type 1 electrocardiogram (ECG) and episodes of syncope are predictors of sudden cardiac arrest in patients with BS.[1-4] However, patients with BS often have autonomic nerve disorders,[5,6] and some of their episodes of syncope can result from low-risk events (such as neurally mediated syncope [NMS] or orthostatic hypotension [OH]). In the general population, NMS has been shown to be one of the major causes of syncope.[7] Although syncopal episodes associated with autonomic dis-

orders usually have prodromal symptoms and occur in specific situations, differentiation of low-risk episodes from high-risk syncopal episodes due to ventricular tachyarrhythmias is often difficult in patients with BS. Moreover, vagal nerve activation causes NMS as well as exaggeration of ST-segment elevation and induces ventricular fibrillation (VF) in patients with BS.[8] It is possible that vagal nerve activation initiates NMS-like symptoms and subsequently induces VF. Determination of the etiology of syncope episodes is important to identify patients with BS who are at risk of sudden cardiac arrest and who require an implantable cardioverter-defibrillator (ICD). When vagal nerve activation induces VF, prodrome accompanied by vagal nerve activation can appear immediately before the episodes. In the present study, we investigated the characteristics of syncope and determined high-risk syncope associated with ventricular arrhythmias to differentiate high-risk syncope episodes from low-risk events. We also determined whether

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patients have any prodrome before VF in association with vagal nerve activation.

Methods

We first enrolled 92 patients with a history of syncope and faintness who had BS-like ECGs. We excluded 7 patients because of inability to confirm type 1 ECG by the consensus report of BS[2] spontaneously or after a drug-provocation test. We also excluded 1 patient with a history of VF due to ischemic heart disease who had undergone coronary-artery bypass surgery for triple vessel disease. Therefore, this study group comprised 82 males and 2 females with BS (mean age 47 $\pm$ 12 years). All patients had episodes of syncope (76 patients) or faintness (8 patients) and had type 1 ECG (61 spontaneous and 23 pilsicainide-induced). We divided the patients into 2 groups according to syncope episodes associated with the existence of prodrome: patients with prodromal symptoms or specific situations (prodromal group; n = 41) and patients without any prodromal symptoms or specific situations (nonprodromal group; n = 43). We defined prodromal symptoms as blurred vision, diaphoresis, palpitations, chest discomfort, and symptoms associated with urination.

No patients were from the same family. Echocardiography and chest radiography were performed in all patients, and no abnormalities were found. We interviewed all patients at the time of history to obtain information on situations and characteristics of syncope. The follow-up duration was defined as the time between the first event and the final visit date. The mean follow-up duration of all patients was 48 $\pm$ 48 months. Syncope was classified on the basis of the European Society of Cardiology guidelines for the diagnosis and management of syncope (version 2009).[9] NMS was diagnosed by the combination of results of a head-up tilt (HUT) test[9] and situations and symptoms of syncopal episodes. Documentation of VF was defined as cardiopulmonary arrest at the hospital or in the ambulance. Detection of VF was defined as records of continuous ECG monitoring, automated external defibrillator, and ICD.

The HUT test[9] was performed in 35 patients (25 patients in the prodromal group and 10 patients in the nonprodromal group). The test was performed in the late afternoon in a fasting state. An intravenous line was inserted before the HUT test. Each patient lay on the tilt table in the supine position for 10 minutes at first. Then the tilt table was kept at an angle of 75° for 20 minutes. When the passive control test result was negative, the patient was returned to the supine position. Thereafter, low-dose isoproterenol infusion ($\approx$0.01–0.03 μg/kg/min) was started to increase the heart rate. After an increase of more than 20% over baseline in the heart rate had been achieved, the tilt table was again kept at an angle of 75° for 25 minutes. A positive HUT test was defined as appearance of syncope or presyncope associated with reflex hypotension or bradycardia. The HUT response was classified as cardioinhibitory, vasodepressor, or mixed type on the basis of the predominancy of cardioinhibitory or vasodepressor reflex.

Standard 12-lead ECGs (0–150-Hz filter) and additional V_1-V_3 at the 3rd intercostal space were recorded simultaneously. We evaluated the RR, PQ, and QRS intervals in lead II as well as the QT interval, ST level at J point, and existence of fragmented QRS (f-QRS) in leads V_1-V_3 of the 12-lead ECG at the patients' first visit. We previously reported that type 0 ECG was defined as coved ST-segment elevation $\geq$ 2 mm with an absent or shallow negative T wave (depth $\leq$ 1 mm)[10] (Figure 1).

The presence of late potential was evaluated with a signal-averaged ECG (ART 1200EPX, noise level < 0.3 μV, and high-pass filtering of 40 Hz with a bidirectional 4-pole Butterworth). The filtered QRS duration, root-mean-square voltage of the terminal 40 ms in the filtered QRS complex, and duration of low-amplitude signals <40 μV in the terminal filtered QRS complex were measured by the signal-averaged ECG. Late potentials (LPs) were considered to be positive when the following 2 criteria were met: root-mean-square voltage of the terminal 40 ms in the filtered QRS complex < 20 μV and duration of low-amplitude signals <40 μV in the terminal filtered QRS complex > 38 ms.[11]

All the patients who underwent an electrophysiological study had received an explanation of the risks involved and had provided written informed consent. The electrophysiological study was performed in 72 patients. All those patients underwent coronary angiography, and none of the patients had significant coronary artery stenosis. Induction of ventricular arrhythmia was attempted by programmed electrical stimulation from the right ventricular apex, right ventricular outflow, and left ventricle, with a maximum of 3 extrastimuli at 2 cycles.[12,13] The criterion for the induction of ventricular arrhythmia was the induction of sustained polymorphic ventricular tachycardia or VF with double or less extrastimuli.

The genetic analysis of SCN5A was performed in 46 patients as previously described[14] in compliance with guidelines for human genome studies of the ethics committee of Okayama University.

Statistics

Continuous data were expressed as means $\pm$ standard deviation. Comparisons among means were performed with a 2-way analysis of variance coupled with Scheffe's test. A comparison of 2 groups was made with the Student t test for unpaired data (patients' data), as appropriate. Categorical data and percentage frequencies were analyzed by using a nonparametric test (Man-Whitney U test). The Fisher exact test was conducted for a comparison of proportions between the groups. Survival and event rates were determined by using the Kaplan-Meier method and compared between the groups with a 2-sample log-rank test. We compared clinical parameters and prognosis between the prodromal and nonprodromal groups, and then we used Cox proportional hazards model to detect risk factors of VF. To examine prognostic values from predictors of VF and determine cutoff values, an analysis of receiver-operating characteristic
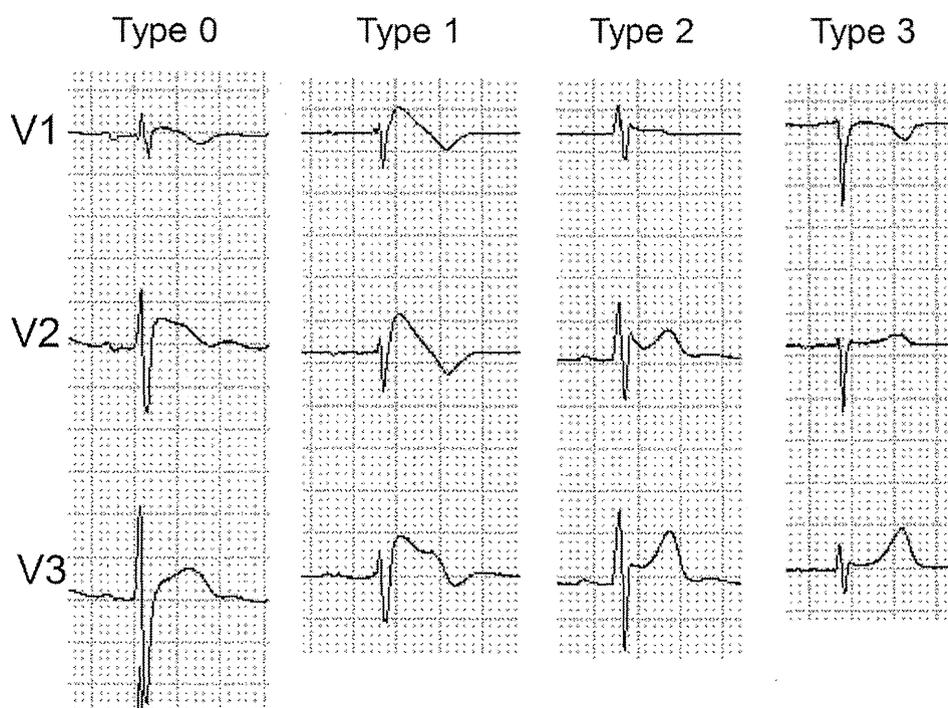
Figure 1   Types of ECGs in patients with Brugada syndrome. **A:** Type 0 is defined as ECG with coved ST-segment elevation ≥ 2 mm and a shallow negative T wave (≤1 mm) or having no negative T wave. **B–D:** Type 1–3 ECGs are defined according to the consensus reports of Brugada syndrome. ECG = electrocardiogram.

curves was done. Significance was defined as $P < .05$. JMP version 7.0 (SAS Institute, Inc, Cary, NC) was used for data analysis.

Results
Clinical characteristics and ECG parameters in the prodromal and nonprodromal groups
There was no difference in the baseline characteristics between the prodromal group and the nonprodromal group (Table 1). VF during the follow-up period in patients without VF documentation at their index hospitalization was more frequent in the nonprodromal group than in the prodromal group (Figure 2A). The percentage of patients in the nonprodromal group who received ICD implantation was higher than that in the prodromal group (Table 1). There were no differences in the inducibility of VF by programmed electrical stimulations, incidence of family history of sudden death, and frequency of SCN5A mutation between the prodromal group and the nonprodromal group. In ECG parameters, the nonprodromal group had a longer PQ interval in lead II and a longer QT interval in lead V_1 than those in the prodromal group. There were no differences in the indices of ECG types and f-QRS between the 2 groups. The filtered QRS interval in the signal-averaged ECG was longer in the nonprodromal group than in the prodromal group.

Features of syncope
Table 2 shows clinical characteristics of syncope. There were no differences in incidences of syncope and faintness between the 2 groups. Patients in the prodromal group

experienced prodrome immediately before episodes of syncope or faintness: blurred vision was the most common prodrome, and about one-third of the patients experienced syncope in association with urination. Abnormal respiration was frequently observed in the nonprodromal group. There were no differences in the frequencies of convulsion, incontinence, and injury between the 2 groups.

Syncope often occurred in the supine position during sleep in patients in the nonprodromal group. Patients in the prodromal group often experienced syncope while they were standing, and this resulted in falling down after the episode. There were no differences in other syncope between the 2 groups. A positive HUT test result was observed more frequently in the prodromal group (54%) than in the nonprodromal group (10%, $P = .012$).

Table 3 shows the clinical characteristics of syncope in patients without VF detection at index hospitalization. When subjects were limited to patients who did not have VF at index hospitalization, blurred vision was the most common prodrome in the prodromal group. The clinical features of these patients' subgroups were similar to the data including patients who had VF at index hospitalization (Tables 2 and 3).

Causes of syncope
At the time of index hospitalization, VF was documented in 19 patients (4 in the prodromal group and 15 in the nonprodromal group) and was not documented in 65 patients (37 in the prodromal group and 28 in the nonprodromal group) (Table 2 and Figure 2A). One patient in the nonpro-

Table 1 Clinical and ECG parameters in patients with and without prodromal symptoms

Variables	Prodromal group	Nonprodromal group	P
Number of patients	41	43	
Clinical parameters			
Age (y)	46 ± 11	48 ± 13	NS
Female gender	1 (2%)	1 (2%)	NS
Family history	11 (27%)	10 (23%)	NS
SCN5A mutation	7/18 (39%)	13/28 (46%)	NS
Inducible VF/VT at PES	19/35 (54%)	19/37 (52%)	NS
Follow-up period (m)	44 ± 42	52 ± 52	NS
ICD implantation	14 (34%)	31 (72%)	.00036
ECG parameters			
ECG type			
Type 1	28 (68%)	33 (77%)	NS
Type 0	16 (39%)	16 (39%)	NS
RR II (ms)	963 ± 164	991 ± 183	NS
PQ II (ms)	170 ± 21	182 ± 27	.029
QRS II (ms)	111 ± 18	112 ± 20	NS
QT			
V_1 (ms)	385 ± 33	403 ± 39	.027
V_2 (ms)	400 ± 39	413 ± 38	NS
V_3 (ms)	393 ± 33	406 ± 38	NS
ST level			
V_1 (mV)	0.19 ± 0.10	0.26 ± 0.26	NS
V_2 (mV)	0.33 ± 0.16	0.41 ± 0.32	NS
V_3 (mV)	0.21 ± 0.09	0.25 ± 0.18	NS
Fragmented QRS			
Number of spikes			
V_1	2.7 ± 0.8	2.8 ± 1.0	NS
V_2	2.5 ± 1.3	3.0 ± 1.2	NS
V_3	2.0 ± 1.1	2.3 ± 1.0	NS
Total spikes	7.2 ± 2.6	8.1 ± 2.7	NS
Existence of f-QRS	14 (34%)	23 (50%)	NS
Signal averaged ECG			
Filtered QRS (ms)	119 ± 16	130 ± 21	.012
LAS40 (ms)	45 ± 14	49 ± 15	NS
RMS40 (μV)	15 ± 9	12 ± 9	NS
Late potential positive	27 (66%)	34 (79%)	NS

Values represent n (%) and mean ± standard deviation.

ECG = electrocardiogram; f-QRS = fragmented QRS; ICD = implantable cardioverter-defribillator; LAS40 = duration of low-amplitude signals <40 μV in the terminal filtered QRS complex; NS = nonsignificant; PES = programmed electrical stimulation; RMS40 = root-mean-square voltage of the terminal 40 ms in the filtered QRS complex; VF = ventricular fibrillation; VT = ventricular tachijcardia.

dromal group who had syncope episodes coincident with bradyarrhythmia was diagnosed as having sick sinus syndrome. Among 64 patients without documented VF at their index hospitalization, we considered causes of syncope to be NMS in 21 patients (all in the prodromal group) and OH in 13 patients (6 in the prodromal group and 7 in the nonprodromal group) on the basis of results of HUT tests and situations of the episodes, but we could not determine the cause of syncope in 30 patients (unexplained syncope: 10 in the prodromal group and 20 in the nonprodromal group). VF was documented at the time of recurrent syncope in 13 patients with unexplained syncope and was more frequent in the nonprodromal group (n = 10) than in the prodromal group (n = 3; P = .044) during the follow-up

period (Figures 2A and 2B). One patient in the nonprodromal group was diagnosed with epilepsy during follow-up. None of the patients diagnosed with NMS or OH experienced VF during follow-up.

Predictors of VF

Table 4 shows results of univariate analysis for the prediction of VF in clinical and ECG parameters between patients with VF and patients without VF. In this table, documentation of VF includes both VF at index hospitalization and VF during the follow-up period. Clinical parameters were not different between patients with documented VF (VF group) and patients without documented VF (non-VF group). In ECG parameters, appearance of spontaneous type 1 or type 0 ECG, prolonged QT interval in leads V_1 and V_2, and existence of f-QRS were associated with the occurrence of VF (Table 4). Although prodrome was usually related to non-VF episodes, about 20% of the patients in the VF group experienced prodrome before the onset of VF (Table 5): prodromal symptoms before VF were blurred vision (rare), palpitations, and chest discomfort. VF often occurred at rest in the supine position and was accompanied by convulsion and abnormal respiration during the episode. Non-VF episodes usually occurred with prodrome (especially blurred vision and diaphoresis) while patients were standing or urinating.

Figures 2B and 2C show results of the Kaplan-Meier analysis of the new occurrence of VF in patients without documented VF at their index hospitalization. Absence of prodrome (especially blurred vision, relation to urination, and diaphoresis) was associated with the subsequent occurrence of VF episodes during the follow-up period (Figure 2C).

Table 6 shows results of univariate analysis for the prediction of VF in patients with BS. Prodromal symptoms (especially blurred vision) and syncope while standing were low-risk symptoms for the occurrence of VF, and syncope without prodrome was a predictor of VF occurrence during follow-up. Abnormal respiration and convulsion during the episode were related to the occurrence of VF. Appearance of type 0 or type 1 ECG and existence of late potential or f-QRS were also predictors of VF.

Multivariate analysis that included the variables listed in Table 6 indicated that syncope with blurred vision was a low-risk symptom for the occurrence of VF and that abnormal respiration and f-QRS were independent risk factors for the occurrence of VF. Receiver-operating characteristic curves for patients with VF showed that absence of blurred vision had high sensitivity (93.8%) but low specificity (50.0%), abnormal respiration had low sensitivity (43.8%) but high specificity (92.3%), and f-QRS had intermediate sensitivity (71.9%) and specificity (73.1%). Figure 2D shows that the receiver-operating characteristic curve was graphed by the combination of fQRS, abnormal respiration, and absence of blurred vision. This combination had an excellent accuracy of diagnosis for patients with VF (sensitivity of 84.4% and specificity of 82.7%).
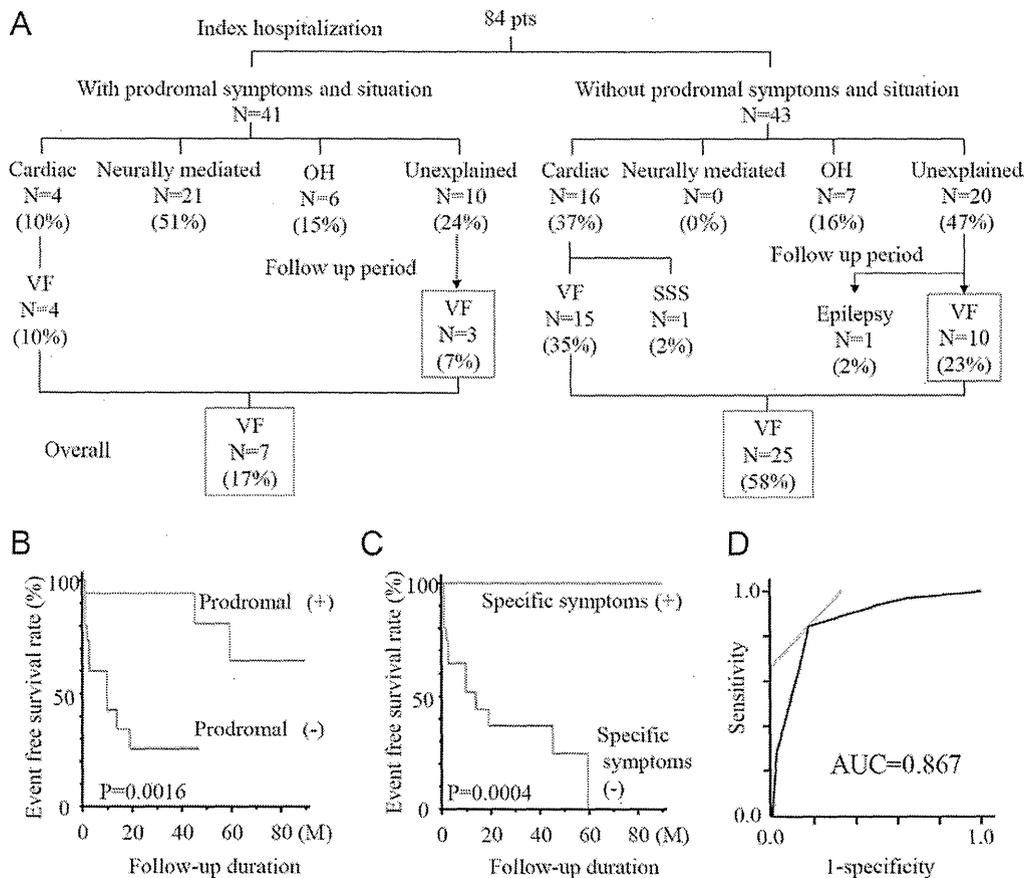
Figure 2   Prognosis and risk factors for the occurrence of VF in patients with Brugada syndrome. **A:** Causes of syncope in Brugada syndrome patients with and without prodromal syndrome and situations at the initial visit and during the follow-up period. **B:** Freedom from lethal arrhythmic events for patients with and without prodromal symptoms and specific situations (blurred vision, relation to urination, diaphoresis, palpitations, and chest discomfort). Patients in the nonprodromal group often experienced recurrence of syncope owing to VF within 2 years from the first visit. **C:** Freedom from events for patients with and without existence of specific symptoms (blurred vision, diaphoresis, and relation to urination). Patients with specific symptoms did not suffer from VF during the follow-up period. **D:** Receiver-operating characteristic curve of the combination of fQRS, abnormal respiration, and absence of blurred vision. This combination was the highest AUC and had excellent accuracy of diagnosis for patients having VF. AUC = area under the curve; f-QRS = fragmented QRS; OH = orthostatic hypotension; SSS = sick sinus syndrome; VF = ventricular fibrillation.

Discussion

New observations

We found that syncope without prodrome was a high-risk sign associated with VF episodes. Although blurred vision, relation to urination, and diaphoresis were not associated with the occurrence of VF, 2 other prodromal symptoms—palpitations and chest discomfort—might be associated with VF episodes. We also found that syncope associated with VF often occurred in the supine position during sleep and was accompanied by convulsion and abnormal respiration. Therefore, absence of prodrome (especially blurred vision) and existence of abnormal respiration and f-QRS were important risk factors for the occurrence of VF in patients with BS and syncope. When syncopal episodes without documented VF at index hospitalization were accompanied by absence of blurred vision and existence of abnormal respiration and fQRS, VF was more likely in follow-up. Although vagal nerve activation can induce VF in patients with BS, patients did not have any vagally induced prodrome before the onset of VF.

Syncope episodes in BS

Previous studies showed that spontaneous type 1 ECG and syncope episodes were predictors of arrhythmic events in patients with BS.[15,16] The FINGER study[17] showed that the cardiac event rate in patients with syncope was lower than that in patients with aborted sudden cardiac death but higher than that in asymptomatic patients. Thus, in previous studies, prognosis for patients with syncope was better than for patients with documented VF, although the syncope could have resulted from VF. This might be due to the fact that syncope episodes include both high-risk episodes related to VF and low-risk benign syncope episodes such as NMS and OH. Yokokawa et al[5] reported that one-third of the patients with BS had NMS, and they concluded that an impaired balance of the autonomic nervous system was related to their syncopal episodes. NMS[6] was also observed in asymptomatic patients with Brugada-type ECG. Thus, an indication for ICD implantation requires confirmation of the mechanism of syncope in patients with BS being benign or not. The HUT test is a useful tool for augmenting vagal

Table 2 Characteristics of syncope in patients with and without prodromal symptoms

Variables	Prodromal group	Nonprodromal group	P
Number of patients	41	43	
Symptom			
Syncope	38 (93%)	38 (88%)	NS
Faintness	3 (7%)	5 (12%)	NS
Prodromes			
Blurred vision	28 (68%)	0 (0%)	<.0001
Relation to urination	11 (27%)	0 (0%)	.00018
Diaphoresis	10 (24%)	0 (0%)	.00042
Palpitation	9 (22%)	0 (0%)	.0009
Chest discomfort	6 (15%)	0 (0%)	.0088
Patients' condition after onset of syncope			
Convulsion	6 (15%)	10 (23%)	NS
Incontinence	4 (10%)	7 (16%)	NS
Falling down	15 (37%)	8 (19%)	NS
Any injury	3 (7%)	2 (5%)	NS
Abnormal respiration	3 (7%)	15 (35%)	.0018
Position at the onset of syncope			
Supine	3 (7%)	18 (42%)	.0002
Sitting	15 (37%)	12 (28%)	NS
Standing	23 (56%)	13 (30%)	.016
Situation at the onset of syncope			
On exertion	1 (2%)	1 (2%)	NS
Standing-up	7 (17%)	7 (16%)	NS
Bathing	4 (10%)	2 (5%)	NS
Rest	7 (17%)	19 (44%)	.0068
Sleeping	3 (7%)	15 (35%)	.0018
Drinking	4 (10%)	6 (14%)	NS
Initial diagnosis of the syncope			
Arrhythmias			
VF	4 (10%)	15 (35%)	.0055
SSS	0 (0%)	1 (2%)	NS
Neurally mediated syncope	21 (51%)	0 (0%)	<.001
Orthostatic hypotension	6 (15%)	7 (16%)	NS
Unexplained	10 (24%)	20 (47%)	.035

Values represent n (%).
NS = nonsignificant; SSS = sick sinus syndrome; VF = ventricular fibrillation.

nerve activity and inducing NMS, but positive results of a HUT test in BS patients with syncope might incorrectly indicate syncope associated with VF as being benign vagal syncope.

Another dilemma related to autonomic nerve activation in BS is that vagal nerve stimulation could aggravate the pathophysiology of BS. Vagal nerve activation mediated by acetylcholine caused abbreviated epicardial action potential and augmented ST-segment elevation in ECGs in an experimental model of BS.[18] Heterogeneous loss of the phase 2 dome of the action potential initiates phase 2 reentry and polymorphic ventricular tachycardia. Infusion of acetylcholine into the coronary artery augmented ST-segment elevation without coronary vasospasm and induced VF.[8,19] Physiological conditions enhanced vagal nerve activity and also

augmented ST-segment elevation in right precordial leads in relation to the occurrence of VF.[20]

Although prodrome was often accompanied by benign syncope[9,21] (such as NMS and OH), arrhythmic syncope had less prodromal symptoms.[22,23] It is difficult to differentiate benign syncope from ventricular tachyarrhythmia in patients with BS because vagal nerve activation can induce NMS as well as VF.[8,19] In the present study, we showed that patients did not have any vagally induced prodrome before the onset of VF. We analyzed prodrome and situations in detail and consequently found that syncope with blurred vision, diaphoresis, or a situation related to urination indicated benign symptoms mediated by NMS or OH in patients with BS. Palpitations and chest discomfort could be prodrome at the onset of VF.

Table 3 Characteristics of syncope in patients without VF detection at index hospitalization between the prodromal group and the nonprodromal group

Variables	Prodromal group	Nonprodromal group	P
Number of patients	37	28	
Symptom			
Syncope	34 (92%)	23 (82%)	NS
Faintness	3 (8%)	5 (18%)	NS
Prodromes			
Blurred vision	26 (70%)	0 (0%)	<.0001
Relation to urination	11 (30%)	0 (0%)	.0060
Diaphoresis	10 (27%)	0 (0%)	.0099
Palpitation	7 (19%)	0 (0%)	.038
Chest discomfort	4 (11%)	0 (0%)	NS
Patients' condition after onset of syncope			
Convulsion	4 (11%)	6 (21%)	NS
Incontinence	4 (11%)	6 (21%)	NS
Falling down	14 (38%)	4 (14%)	.0256
Any injury	3 (8%)	2 (7%)	NS
Abnormal respiration	3 (8%)	6 (21%)	NS
Position at the onset of syncope			
Supine	2 (5%)	13 (46%)	.0002
Sitting	5 (18%)	12 (32%)	NS
Standing	23 (62%)	10 (36%)	NS
Situation at the onset of syncope			
On exertion	1 (3%)	1 (4%)	NS
Standing-up	7 (19%)	7 (25%)	NS
Bathing	3 (8%)	1 (4%)	NS
Rest	5 (14%)	15 (54%)	.0001
Sleeping	2 (5%)	11 (39%)	.0007
Drinking	3 (8%)	4 (14%)	NS
Initial diagnosis of the syncope			
Arrhythmias			
VF	0 (0%)	0 (0%)	–
SSS	0 (0%)	1 (4%)	NS
Neurally mediated syncope	21 (57%)	0 (0%)	<.0001
Orthostatic hypotension	6 (16%)	7 (25%)	NS
Unexplained	10 (27%)	20 (71%)	.014

Values represent n (%).
NS = nonsignificant; SSS = sick sinus syndrome; VF = ventricular fibrillation.

Table 4 Clinical and ECG parameters in patients with and without VF

Variables	VF	Non-VF	P
Number of patients	32	52	
Clinical parameters			
Age (y)	49 ± 11	47 ± 13	NS
Female gender	1 (3%)	1 (2%)	NS
Family history	9 (28%)	12 (23%)	NS
SCN5A mutation	12/24 (50%)	8/22 (36%)	NS
Inducible VF/VT at PES	16/30 (53%)	21/42 (50%)	NS
Follow-up period (m)	68 ± 55	36 ± 38	.0024
ICD implantation	29 (91%)	16 (31%)	<.0001
ECG parameters			
ECG type			
Type 1	29 (91%)	32 (62%)	.0032
Type 0	19 (59%)	13 (25%)	.0014
RR II (ms)	991 ± 145	970 ± 189	NS
PQ II (ms)	177 ± 32	176 ± 20	NS
QRS II (ms)	115 ± 22	109 ± 17	NS
QT			
V_1 (ms)	410 ± 36	384 ± 35	.0018
V_2 (ms)	422 ± 37	397 ± 37	.0055
V_3 (ms)	404 ± 38	397 ± 34	NS
ST level			
V_1 (mV)	0.24 ± 0.15	0.22 ± 0.22	NS
V_2 (mV)	0.35 ± 0.22	0.38 ± 0.28	NS
V_3 (mV)	0.21 ± 0.12	0.24 ± 0.15	NS
Fragmented QRS			
Number of spikes			
V_1	3.0 ± 0.9	2.6 ± 0.9	NS
V_2	3.4 ± 1.2	2.4 ± 1.2	.0005
V_3	2.4 ± 1.1	2.0 ± 1.1	NS
Total spikes	8.8 ± 2.4	6.9 ± 2.6	.0014
Existence of f-QRS	23 (72%)	14 (27%)	<.0001
Signal averaged ECG			
Filtered QRS (ms)	132 ± 19	121 ± 18	.0099
LAS40 (ms)	53 ± 16	44 ± 13	.014
RMS40 (μV)	11 ± 9	15 ± 8	.020
Late potential positive	27 (84%)	34 (65%)	NS

Values represent n (%) and mean ± standard deviation.

ECG = electrocardiogram; f-QRS = fragmented QRS; ICD = implantable cardioverter-defribillator; LAS40 = duration of low-amplitude signals <40 μV in the terminal filtered QRS complex; NS = nonsignificant; PES = programmed electrical stimulation; RMS40 = root-mean-square voltage of the terminal 40 ms in the filtered QRS complex; VF = ventricular fibrillation; VT = ventricular tachijcardia.

Generally, symptoms with prodrome resulted from benign syncope in relation to autonomic dysfunction and were not associated with the occurrence of VF in patients with BS. Although the present study showed that the clinical course of syncope episodes with prodrome was benign, we should emphasize that the existence of NMS and OH in patients with BS cannot predict whether patients will have new onset of VF in the future.

Limitations

We selected patients with type 1 ECG and a history of syncope. Their causes of syncope were classified as documented VF, NMS, OH, and unexplained syncope. However,

unexplained syncopal episodes could include different forms between low-risk events (ie, NMS and OH) and high-risk events (ie, VF). The FINGER study[17] indicated that symptomatic patients more frequently underwent ICD implantation than did asymptomatic patients. The second consensus report[2] showed that confounding factors affecting ECG abnormality or syncope should be carefully excluded. Although this report described different factors of ECG abnormality in detail, the clinical features of various types of syncope episodes were not described. In this study, the unexplained syncope group would be patients of high risk for VF and they underwent ICD implantation prophylactically. As a result, they had an appropriate discharge of ICD and sudden cardiac death was prevented.

The results of the HUT test were more frequently positive in the prodromal group than in the nonprodromal group. However, we could not perform the HUT test in all patients with VF, especially in patients in whom VF or aborted cardiac arrest was documented at index hospitalization. Therefore, the number of patients who took a HUT test was limited and a positive HUT test result was not a significant predictor of VF. Although there were no patients with a positive HUT test result in the VF group, it could not be concluded in this study that a tilt test confirms benign syncope in patients with Brugada-type ECG.

Table 5 Characteristics of syncope in patients with and without VF

Variables	VF	Non-VF	P
Number of patients	32	52	
Syncope			
Prodromes			
If any	7 (22%)	35 (67%)	<.0001
Blurred vision	2 (6%)	26 (50%)	<.0001
Relation to urination	0 (0%)	11 (21%)	.0049
Diaphoresis	0 (0%)	11 (21%)	.0049
Palpitation	4 (13%)	5 (10%)	NS
Chest discomfort	4 (13%)	2 (4%)	NS
Patients' condition after onset of syncope			
Convulsion	13 (41%)	3 (6%)	<.0001
Incontinence	6 (19%)	5 (10%)	NS
Falling down	7 (22%)	16 (30%)	NS
Any injury	0 (0%)	5 (9%)	NS
Abnormal respiration	14 (44%)	4 (8%)	<.0001
Position at the onset of syncope			
Supine	14 (43%)	7 (13%)	.0016
Sitting	13 (41%)	14 (27%)	NS
Standing	5 (16%)	31 (60%)	<.0001
Situation at the onset of syncope			
On exertion	2 (6%)	0 (0%)	NS
Standing-up	0 (0%)	14 (27%)	.0011
Bathing	2 (6%)	4 (8%)	NS
Rest	15 (47%)	11 (21%)	.013
Sleeping	13 (41%)	5 (10%)	.0006
Drinking	4 (13%)	6 (12%)	NS

Values represent n (%).

NS = nonsignificant; VF = ventricular fibrillation.

Table 6 Univariate and multivariate analyses in all patients

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Prodomes						
If any	0.24	0.09–0.57	.0008	–		
Blurred vision	0.11	0.02–0.37	<.0001	0.20	0.03–0.75	.0145
Abnormal respiration	3.26	1.55–6.81	.0023	2.18	1.02–4.64	.045
Convulsion	2.40	1.15–4.86	.021	–		
Syncope while standing	0.37	0.13–0.89	.025	–		
Type 1 ECG	3.86	1.37–16.1	.0078	–		
Type 0 ECG	2.57	1.27–5.34	.0083	–		
Late potential positive	2.85	1.19–8.44	.018	–		
Existence of f-QRS	3.57	1.70–8.19	.0006	2.39	1.11–5.62	.0261

CI = confidence interval; ECG = electrocardiagram; f-QRS = fragmented QRS; HR = hazard ratio.

Conclusion

Syncope episodes with prodromal symptoms and specific situations, especially blurred vision, are benign symptoms in patients with BS. Absence of prodrome is a high-risk sign of the occurrence of VF in BS patients with syncope episodes.

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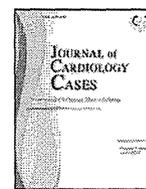
Editorial

The compound mutation, a model for acquire long QT syndrome

Congenital long QT syndrome is a relatively rare disease and it has been reported that its incidence is 1:2000 [1]. Mutations that cause long QT syndrome usually alter cardiac repolarization currents and prolong action potential duration. Most of the patients have one mutation but some patients have two or more mutations simultaneously. From the general incidence of long QT syndrome, the theoretical frequency of patients with compound mutations will be 0.05% of the patients, but the real frequency is up to 9% of the probands [2–6]. Although the family members who have one of the mutations often have mild phenotype and relatively benign clinical course, probands who have compound mutations show more severe clinical phenotypes. Previous reports demonstrated that patients with compound mutations had longer QT interval [2,5,6], younger age at onset of the cardiac event [2,5], and were more likely to have cardiac arrest [2,4,6] than patients with a single mutation. Indeed, a patient reported by Ito et al. had markedly long QT interval with bizarre T wave morphology, and experienced aborted cardiac arrest [7].

Cardiac repolarization is regulated by periodical activation and inactivation of cardiac ion channels [8]. Inward currents by sodium (I_{Na}) and calcium ions (I_{Ca}) depolarize myocytes and outward currents by some potassium currents (I_{to}, I_{Kr}, I_{Ks}, and I_{K1}) repolarize myocytes to resting membrane potential. Disruption of the balance of the outward and inward currents prolongs action potential duration and then causes QT interval prolongation. Prolongation of the action potential duration results in calcium overload in the myocytes and inward depolarizing current by calcium ion initiates early after depolarization and triggered activity. Experimental studies have shown compound ion channel dysfunction promotes occurrence of torsades de pointes (TdP). Emori and Antzelevitch initially reported that the combination of the potassium current dysfunction by I_{Kr} (LQT2 model) and I_{Ks} blockers (LQT1 model) reproduced clinical phenotypes of acquired long QT syndrome and this can be applied to compound mutations [9]. After this report, others showed that a combination of blockers of the potassium currents and/or enhancers of the late sodium current in experimental models reproduced clinical phenotypes of compound mutations [10–12]. Although relatively low doses of a single drug alone had mild effects on cardiac repolarization and did not initiate TdP, a combination of these drugs prolonged action potential duration and QT interval, and frequently promoted TdP. Because several ion currents contribute to cardiac repolarization, mild to moderate dysfunction of an ion channel can be clinically latent. A combination of two or more dysfunctional ion channels results in the loss of repolarization reserve [13] and unmasks the prolongation of the repolarization phase.

Although the incidence of compound mutations is more frequent than that of expected theoretically, it is rare to diagnose patients with compound mutations in daily clinical practice. But two or more dysfunctioning ion channels frequently occur in elderly patients with long QT syndrome. Elderly patients have many chances to take drugs for various diseases. Mineral abnormalities, especially hypokalemia, can frequently occur from gastrointestinal, renal, or nutritional disorders. Drugs that prolong QT interval usually block I_{Kr} current and hypokalemia blocks both I_{Kr} and I_{K1}; the combination of these reduces the repolarization reserve. Existence of organic heart disease, heart failure, and bradycardia also alter the ion channel functions and prolong QT interval. In patients with congenital long QT syndrome, young patients often experience syncope or TdP by adrenergic stimulation (such as exercise and loud noise), but adrenergic stimulation as proarrhythmic triggers is less frequent in elderly patients. TdP often occurs by secondary triggers as hypokalemia, bradycardia, and drugs in elderly patients [14]. If patients have a single mutation, acquired triggers add the second ion channel dysfunction and eliminate repolarization reserve, then promote TdP. Compound ion channel dysfunctions can frequently occur in elderly patients with long QT syndrome.

In patients without mutations, compound ion channel dysfunctions can cause acquired long QT syndrome. Predisposing factors for acquired QT prolongation are female gender, age, drugs, mineral abnormalities, organic heart disease, arrhythmias, severe visceral dysfunction, and QT prolongation at baseline. Accumulation of predisposing factors markedly reduces repolarization reserve and increases the incidence of cardiac events [15]. Indeed, patients with syncope/TdP have more multiple predisposing factors at the time of QT prolongation than do asymptomatic patients. Patients with acquired long QT syndrome have complex T wave resembling electrocardiograms in animal models of compound ion channel dysfunction [9,10] and in patients with compound mutations. Compound mutations in patients result in a rare severe form of long QT syndrome, but it will be a clinical model of acquired long QT syndrome or elderly patients with a single mutation and secondary trigger.

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