stomach, fever, glucose insulin test, etc.[17–20,22,26]) caused ECG alterations in the patients, we emphasize that spontaneous ECG alterations *without any stress* often occurred in the patients with a high risk of VF. Patients who had long-term ECG alterations also were likely to have spontaneous AP heterogeneity that causes ECG alterations and VF.

Previously, we showed that the presence of fQRS was a risk factor for developing VF in patients with VF or syncope.[12] From that study and the present one, it is clear that both depolarization and repolarization abnormalities can contribute to the onset of ventricular arrhythmias in BS.

Limitations

We selected elderly patients with Brugada-type ECG as a VF− group. Priori et al[3] showed that the age of the first VF attacks in patients with BS was 33 years (range 2 months to 55 years)[2] and that new onset of VF was infrequent in the elderly population. Although the incidence of new-onset VF in asymptomatic patients is still controversial,[2,5] including patients younger than 60 years old in the VF− group could mix in some high-risk patients who would experience VF in the future. Among asymptomatic patients, the elderly were more likely VF−free survivors and thus have a much lower possibility of developing VF than younger patients. However, the effects of aging in BS have not been well characterized,[2] and thus long-term follow-up should be necessary in this population. Further, the ECG parameters in this study should be applied in a new study to a young BS population.

In the *in vitro* experiments, we recorded transmural ECGs with electrodes (diameter ~1 mm) at a ~5 mm distance from the isolated tissues. In contrast, the clinical ECG electrodes have a large surface area (≈2–3 cm^2) and are placed on the body surface ~4–5 cm from the epicardium). Thus, clinical ECG electrodes could be less sensitive to local changes within the RV epicardium. The observed alterations in clinical ECGs reflected electrophysiological changes within a larger tissue mass than in the *in vitro* tissue model of BS.

Conclusion

These clinical and experimental studies indicate that prominent ECG repolarization alterations (conversion between type 0, 1, and normal ECGs) are a risk factor for the occurrence of VF in older patients with BS because they suggest the presence of AP heterogeneity within the RV epicardium, leading to the initiation of phase 2 reentry and occurrence of polymorphic VT.

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〈講演1〉

Brugada症候群に合併したVF stormに対するベプリジルの効果

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はじめに

Brugada症候群は、右側胸部誘導心電図において特徴的なST上昇を呈する特発性心室細動（VF）で、突然死の原因疾患の1つである。Brugada症候群のVF既往例または心停止後蘇生例ではVF再発率が33%にのぼるとの報告もあり[1]、突然死を予防するために植込み型除細動器（ICD）による治療が行われる。しかし、ICD植え込み後も、VFが続発するelectrical stormによりICDが頻回に作動する症例が多い。このため薬物治療によってVFを予防し、ICDの頻回作動を抑制する必要がある。

ICD植え込み後の心室細動予防を目的とした薬物治療

Brugada症候群に対する薬物治療としては、electrical storm出現時の急性期治療とその後のVFの予防を目的とした慢性期治療がある。

急性期治療

Electrical stormは、重症心疾患の際に出現する治療可能な再発性心室不整脈で、ICD植え込み例においては、連続24時間以内に3回以上ICDによる除細動が行われた場合とされている。Brugada症候群でelectrical stormが出現した症例に対しては、突然死を回避するためVFの再発予防を速やかに行う必要がある。Brugada症候群の急性期薬物治療では、カテコラミン製剤であるイソプロテレノールが用いられる。われわれも、不整脈発作を呈するBrugada症候群に対して低用量イソプロテレノール（0.15μg/分）を持続注入することによりST上昇が改善されたことを報告している[2]。

慢性期治療

慢性期のVF抑制に用いられる主な薬剤には、ベプリジル、キニジン、デノパミン、ジソピラミド、シロスタゾールがある。このうちNa^+チャネル遮断薬であるキニジンはVFに対する有効性が確立されており、世界で広く使用されているが、血小板減少や下痢などの副作用が高頻度で発現する[3]。また、わが国におけるキニジンの承認用量は200～600mg/日であり、海外で有効性が報告されている用量600～1,400mg/日でキニジンを使用することはできない。一方で、低用量キニジンによるVF抑制は44%と十分ではない[4]。したがって、有効性が高く副作用は少ない薬剤が望まれており、ベプリジルはこのような条件を満たす薬剤として期待されている。

ベプリジルによる心室細動抑制効果

Brugada症候群を含む特発性VFに対するベプリジルの有効性がわが国で報告されているが[5]、より多くのエビデンスの集積が必要である。また、Brugada症候群の病態に関与するとされる*SCN5A*遺伝子変異の有無がベプリジルの治療効果に及ぼす影響も明らかではない。そこでわれわれは、頻回なVFに対しベプリジルを投与したBrugada症候群7例における治療効果を*SCN5A*遺伝子変異の有無別に後ろ向きに検討した[6]。対象の平均年齢は47歳、全例が男性で、ICD植え込み術が施行されていた。*SCN5A*遺伝子変異陽性は3例、変異陰性は4例であった。心臓突然死の家族歴は、変異陽性例では0例、変異陰性例では2例に認められた。投与開始時の用量はベプリジル100mg/日の低用量とし、効果不十分な場合は1カ月後に200mg/日まで増量した。ベプリジルによるVF抑制効果は、12誘導心電図（ECG）と体表面加算平均心電図（SAECG）を用いて、治療前と治療1カ月後に記録し、検討した。

表　ベプリジルの心室細動抑制効果

症例	治療前			治療後		
	VF（イベント）	観察期間（月）	発現頻度（イベント/月）	VF（イベント）	観察期間（月）	発現頻度（イベント/月）
1	22	72	0.31	0	39	0.00↓
2	11	38	0.29	1	42	0.02↓
3	10	26	0.38	1	31	0.03↓
4	4	13	0.31	3	1	3.00↑
5	10	27	0.37	3	4	0.75↑
6	2	2	1.00	6	1	6.00↑
7	2	49	0.04	2	1	2.00↑

*SCN5A*遺伝子変異 陽性（n=3）：治療前 0.33回/月、治療後 0.02回/月、$p<0.01$
*SCN5A*遺伝子変異 陰性（n=4）：治療前 0.43回/月、治療後 2.94回/月、p=NS

mean±SD、Student *t* 検定

Murakami M, et al. J Cardiovasc Pharmacol 2010; 56: 389-395 より改変.

その結果、治療前後におけるVFの平均発現頻度は、変異陽性例において有意に減少した(0.33回/月 vs. 0.02回/月、$p<0.01$)。一方、変異陰性例においては、VFの平均発現頻度に変化が認められなかった(0.43回/月vs. 2.94回/月、p=NS)(**表**)。また、1肋間上方の第3肋間V_1誘導ECGにおいてJ点のST波高の変化を検討したところ、変異陽性例では治療開始前から低かったST波高が治療後有意に低下したが($p<0.05$)、変異陰性例では同様の変化が認められなかった(**図1**)。QTc間隔については、変異陽性例の全例で延長したのに対し、変異陰性例では2例で短縮し、残り2例では延長していた。さらに、SAECGにおける心室遅延電位(late potential)の指標であるF-QRS、LAS_{40}、RMS_{40}はいずれも変異陽性例で改善したが、変異陰性例では改善しなかった(**図2**)。すなわち、ベプリジルは*SCN5A*遺伝子変異を有するBrugada症候群に対してはVF再発抑制効果を示し、ECGとSAECGの各指標を改善したが、遺伝子変異のないBrugada症候群ではその効果が一様ではなかった。

Brugada症候群では、Na^+電流(I_{Na})が減少している一方で一過性外向きK^+電流(I_{to})が過剰になっており、そこに他の内向きCa^{2+}電流(I_{Ca})の減少やATP感受性K^+電流の増加が加わることによりST上昇をきたすと考えられている。ベプリジルはCa^{2+}チャネルだけでなくNa^+およびK^+チャネルも遮断するマルチチャネルブロッカーであり、I_{to}の増加を濃度依存的に抑制し、低心拍時のQT間隔短縮を改善する。また、I_{Na}を増加させる慢性効果に関する報告もされている[7]。したがって、生来的にI_{Na}が著しく減少している*SCN5A*遺伝子変異陽性例にベプリジルを投与すると、I_{Na}が増加しVF抑制につながると考えられる。一方、変異陰性例のBrugada症候群の病態は多岐にわたるため、ベプリジルが有効な場合もあれば無効な場合もある。今後、症例を蓄積してさらなる検討が望まれる。

文献

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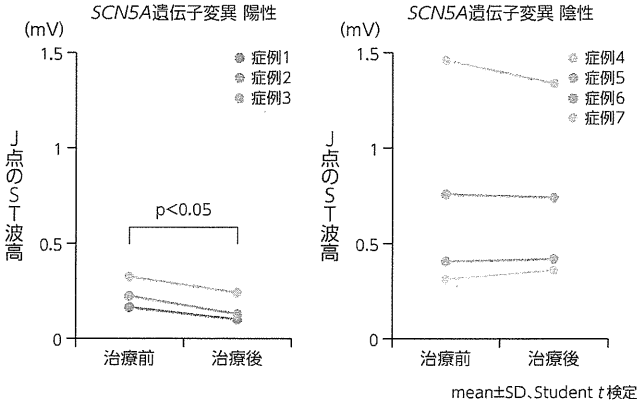
図1 第3肋間V_1誘導でみたJ点のST波高の変化



mean±SD、Student *t* 検定

Murakami M, et al. J Cardiovasc Pharmacol 2010; 56: 389-395.

質疑応答

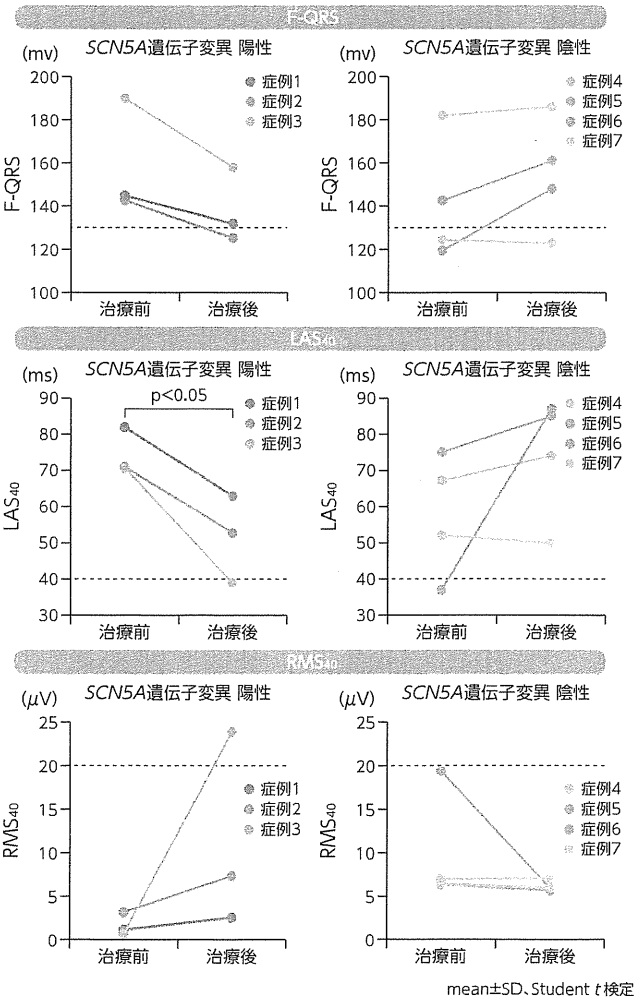
小林(座長) ベプリジルが*SCN5A*遺伝子変異陽性例にVF再発抑制効果を示すということは、心臓興奮伝導障害が強い患者に対しては、より効果を発揮するということでしょうか。

草野 *SCN5A*遺伝子変異陽性例ではI_{Na}が減弱しているので伝導障害が前面に出ていると思われます。ベプリジルはこのような症例のNa^+チャネルだけでなく、他のチャネルや活動電位に総合的に作用し、抗不整脈効果を示すと推察されます。

小林(座長) 実地臨床ではすべての患者に遺伝子検査を行い*SCN5A*遺伝子変異の有無を確認することは困難です。その場合、Brugada症候群でベプリジルの効果が期待される症例の判断をどのようにしてつけますか。

草野 実地臨床では、ピルシカイニド負荷試験が有用であると思います。ピルシカイニド負荷試験でQRS間隔延長やPQ間隔延長がみられ、*SCN5A*遺伝子変異が疑われた症例に対しベプリジルを投与したところ、治療効果が確認されました。Brugada症候群に特徴的な心電図変化の有無と臨床所見から適応例を見分けられる可能性があります。

図2 体表面加算平均心電図における各指標の変化



mean±SD、Student *t* 検定

Murakami M, et al. J Cardiovasc Pharmacol 2010; 56: 389-395.

症例

Brugada型心電図所見を呈し不整脈源性右室心筋症との関連が示唆された2症例

Two patients with Brugada-type electrocardiogram related with arrhythmogenic right ventricular cardiomyopathy

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《Abstract》

Brugada型心電図を示し，不整脈源性右室心筋症(arrhythmogenic right ventricular cardiomyopathy；ARVC)との関連が示唆された2例を経験したので報告する．症例1は，62歳，男性．前胸部の不快感と心電図異常のため当院へ紹介入院となった．心電図ではST上昇をV_1からV_3で認め，$V_{1\sim2}$誘導ではcoved型を示していた．加算平均心電図法による心室遅延電位(late potential；LP)，T波交互脈(T wave alternans；TWA)は陽性で，電気生理学的検査(electrophysiologic study；EPS)で心室細動(ventricular fibrillation；VF)が誘発された．しかし，CTで右室流出路に脂肪変性を伴う心室瘤を認めARVCとの関連が示唆された．症例2は，77歳，男性．安静時の心肺停止で蘇生例である．心電図で完全右脚ブロックを伴うsaddleback型のST上昇がV_2誘導でみられ，EPSでVFが誘発された．しかし，CTで右室壁の脂肪変性が疑われARVCとの関連が示唆された．今回の2例はいずれもBrugada症候群の好発年齢よりは高齢であり器質的心疾患除外のために施行したCT検査でARVCとの関連が示唆された．高齢でBrugada型心電図所見を呈するものの中には，ARVCと関連する症例群が存在する可能性が示唆された．

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Key words
- Brugada型心電図
- 不整脈源性右室心筋症
- 高齢者
- 心室細動

(2011.3.25 原稿受領；2011.8.25 採用)

はじめに

心室細動(ventricular fibrillation；VF)により心臓突然死をきたす若年例での心電図の特徴として，右脚ブロックや右側胸部誘導におけるST上昇があり，これらの中にはBrugada症候群や不整脈源性右室心筋症(arrhythmogenic right ventricular cardiomyopathy；ARVC)が含まれる[1)]．Brugada症候群は1992年にBrugadaらにより報告され，明らかな器質的心疾患，電解質異常，QT延長がなく，安静時の12誘導心電図上，右側胸部誘導($V_{1\sim3}$)でST上昇を示し，VFを発症する症例群であり[2)]，心筋Naチャネルの蛋白をコードする*SCN5A*遺伝子変異を18～30%に認める疾患である[3)]．

一方，ARVCは，組織学的に右室心筋が脂肪と線維組織に置き換わり右室拡大や収縮不全を呈し，心室性不整脈による突然死や，反復持続する心室性不整脈や心筋障害により心不全が生じる疾患である．約

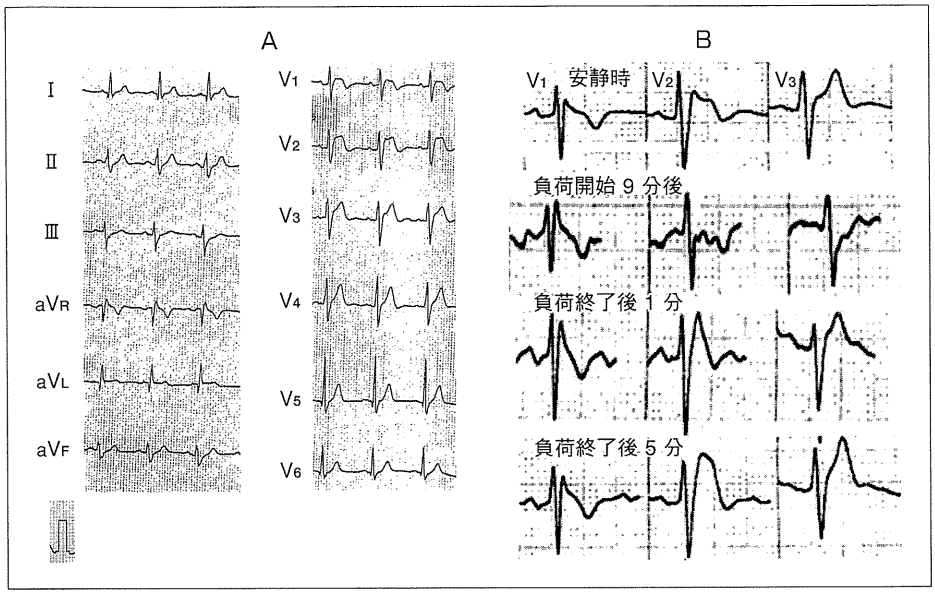

図 1
症例 1 心電図所見
A：入院時心電図所見；洞調律QRS幅118ms，R-R間隔681ms，脈拍70/分．$V_{1\sim3}$でST上昇を認め，$V_{1\sim2}$ではcoved型ST上昇を示している．
B：Treadmil運動負荷心電図所見；安静時・運動負荷試験後に$V_{1\sim3}$でST上昇を認める．

20～30%の症例に遺伝的な背景があることが明らかになってきている[4)5)]．このように，Brugada症候群とARVCは心室性不整脈を呈すること以外は異なる疾患単位であるが，12誘導心電図で典型的なBrugada型心電図所見を呈しながら，CT・MRIなどの画像診断や組織診断でARVCに非常によく似た形態・病理像を示す症例の報告が散見される[6)7)]．今回，われわれは，Brugada型心電図所見を呈し，CTで画像診断上，ARVCが疑われた比較的高齢の2例を経験したので報告する．

症例

1．症例 1

患者：62歳，男性．

主訴：前胸部不快感．

現病歴：1989年ころから明け方や運転中に首から前胸部にかけて焼けるような不快感を自覚していた．近医で精査されたが異常は指摘されなかった．1998年夏ごろから同様な症状が再発したため，再度，近医受診したところ心電図異常を指摘され，精査目的で当院紹介となった．

家族歴：祖母；突然死，母；心臓死（詳細不明）．

既往歴：特記すべきことなし．

入院時現症

身長174cm，体重81kg，血圧120/82mmHg，脈拍70/分・整，意識清明，眼瞼結膜に貧血なし，頸部血管雑音を聴取せず．胸部；心音純，心雑音なし，呼吸音正常，ラ音聴取せず，腹部異常所見なし，両下肢浮腫なし，他異常所見なし．

入院時血液・尿所見：特記すべき異常なし．

入院時心電図所見：洞調律でQRS幅118ms，R-R間隔681ms，$V_{1\sim3}$でST上昇を認める．$V_{1\sim2}$誘導ではcoved型ST上昇を示していた（**図 1**）．

負荷心電図所見：Treadmil運動負荷（Bruce法）心電図検査を施行したところ，負荷開始後にST部分の低下がみられ，負荷終了後にはST部分の上昇が認められ，高risk群の症例であると考えられた（**図 1**）．

心臓超音波検査所見：左房径46mm，左室拡張末期径60mm，左室収縮末期径38mm，EF 69%，軽度の僧帽弁逆流を認める．右室の拡張は認めない．

心室遅延電位（late potential；LP）：陽性（f-QRS：125ms，RMS_{40}：13.5μV，LAS_{40}：46ms）．

当院では，3項目中（f-QRS＞120ms，RMS_{40}＜20μV，LAS_{40}＞38ms）2項目以上を満たした場合をLP陽性としている．

T波交互脈（T wave alternans；TWA）：陽性（V_4誘

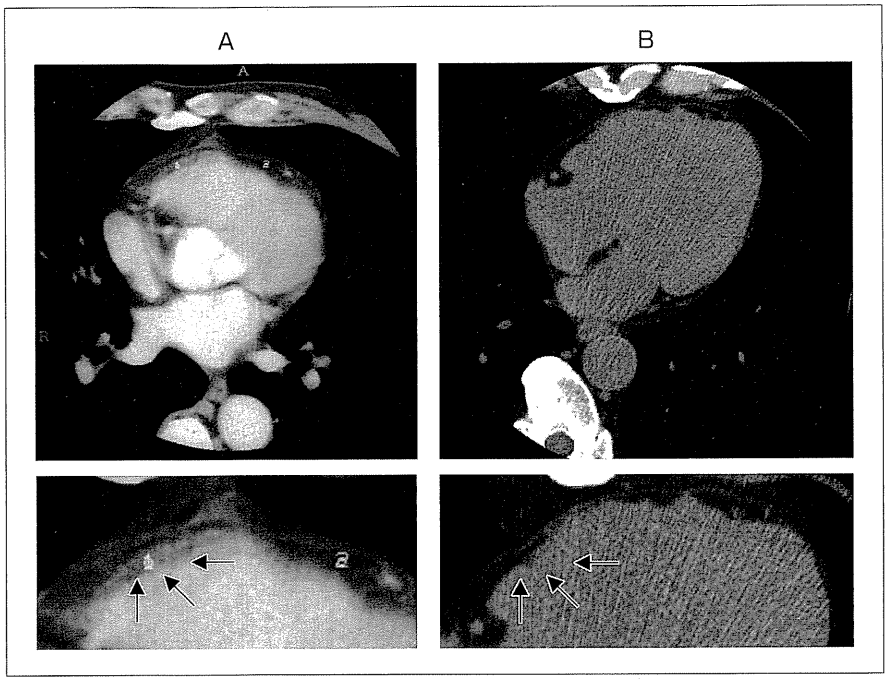

図 2
心電図同期胸部ヘリカルCT所見
A：症例 1 では，収縮期に右室心尖部が瘤状に突出する形態異常を認め，さらに右室にCT値−30.8HUの脂肪変性を疑う低吸収域を認める．
B：症例 2 では，右室壁にCT値−43.0HUの脂肪を示唆する線状の低吸収域を認める．

導でmax Valt 4.4μV，max Ralt 9.0μV)．

冠動脈造影・左室造影検査所見：正常冠動脈であり，明らかな左室壁運動異常を認めない．

心電図同期胸部ヘリカルCT所見：収縮期に右室心尖部が瘤状に突出する形態異常を認める．また，右室流出路の心筋のCT値が−30.8HUと低値を示し，心筋の脂肪変性が疑われる(**図 2**)．

電気生理学的検査(electrophysiologic study；EPS)所見：通常の心室プログラム刺激(心室筋の不応期まで施行)やイソプレテレノール投与後の心室プログラム刺激でもVFは誘発されなかったが，edrophonium 10mg投与後，右室流出路からの 2 連早期刺激(500/250/200ms)でVFは再現性をもって誘発された(**図 3**)．

なお，Brugada症候群の心室性不整脈発作は夜間・安静時など副交感神経緊張時に出現することが知られているため，コリン作動薬(抗コリンエステラーゼ薬)であるedrophoniumを投与し頻拍の誘発を行った．

入院後経過

突然死の家族歴があり，心電図検査所見およびEPSでVFが誘発されたことから本人と相談のうえ，植込み型除細動器(implantable cardioverter defibrillator；ICD)の植え込みを施行した．現在(11年経過)まで外来で経過観察であるが，ホルター心電図で最大 5 連までの非持続性心室頻拍(nonsustained ventricular tachycardia；NSVT)が記録されているが，抗頻拍ペーシングが作動することもなく，VFは記録されていない．現在，外来で経過観察中だが，抗不整脈薬を含めた内服加療は特に行っていない．

2. 症例 2

患者：77歳，男性．

主訴：ICD植え込み目的．

現病歴：教会で礼拝中に突然意識消失・失禁した．Bystandar心肺蘇生法(cardiopulmonary resuscitation；CPR)で心拍再開し前医に救急搬送された．諸検査の結果，Brugada症候群によるVFに伴う意識消失発作と診断され，ICD植え込み目的で当院紹介入院となった．

家族歴：父親がペースメーカー植え込み術施行を施行されているが原疾患を含め詳細不明．そのほか突然死の家族歴はない．

既往歴：73歳時，前立腺肥大症，75歳時，腰部脊

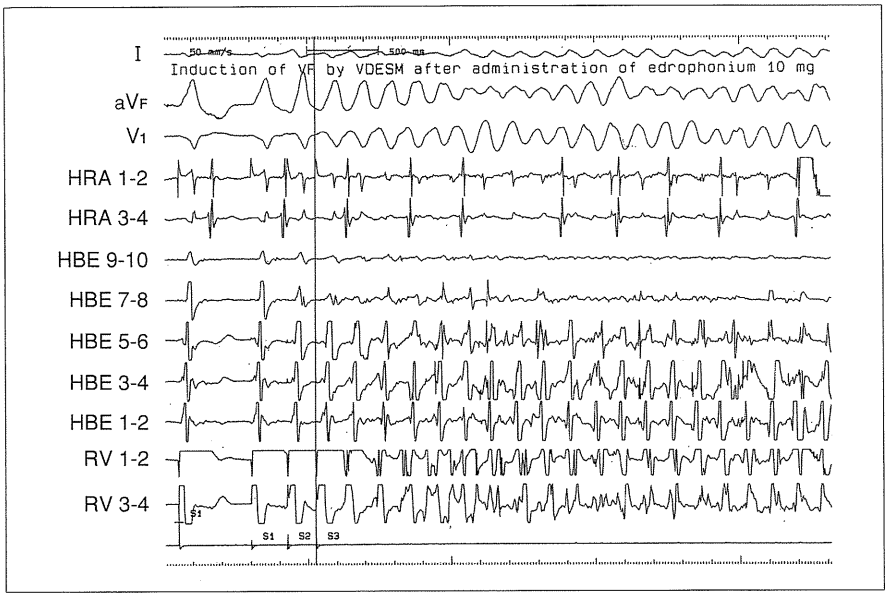

図 3
Edrophonium 10mg投与後，右室流出路からの2連早期刺激(500/250/200ms)で心室細動は再現性をもって誘発された．

柱管狭窄症．特に内服加療など行っていない．

入院時現症

身長162cm，体重64kg，血圧140/64mmHg，体温；36.2℃，脈拍；70/分・整，意識清明，眼球結膜黄染なし，眼瞼結膜貧血なし．胸部；心音純・心雑音なし，呼吸音正常，腹部異常所見なし，神経学的異常所見なし，他特記すべき異常所見なし．

入院時血液検査所見：中性脂肪の上昇を認める以外に特記すべき異常はない．

入院時心電図所見：洞調律でQRS幅160ms，R-R間隔1,000ms，V_2でsaddleback型のST上昇を認め，QRS波直後にノッチを認める1肋間上での心電図はV_2でST部分がcoved型への変化を示しコントロールの心電図同様QRS波直後にノッチを認めた(**図 4**)．

負荷心電図所見：ピルジカイニド負荷後V_2でST部分がcoved型へと変化した．

心臓超音波検査所見：左房径45mm，左室拡張末期径45mm，左室収縮末期径22mm，EF 84%，右室の拡張は認めない．

LP：ピルジカイニド負荷前後ともにLP陽性(負荷前；f-QRS：173ms，RMS_{40}：15.7μV，LAS_{40}：37ms，負荷後；f-QRS：208ms，RMS_{40}：8.4μV，LAS_{40}：68ms)．

TWA：陰性(V_1誘導でmax Valt 1.78μV，max Ralt 10.28μV)．

冠動脈造影・左室造影検査所見：正常冠動脈であり，明らかな左室壁運動異常を認めない．

心電図非同期胸部ヘリカルCT所見：右室壁にCT値－43.0 HUの脂肪を示唆する線状の低吸収域を認める(**図 2**)．

EPS：右室心尖部からの3連早期刺激(400/270/210/200ms)でVFが誘発された(薬剤負荷はなし)(**図 5**)．

入院後経過：心肺停止の蘇生例であり，各種検査所見からもICD植え込み適応と判断してICDを植え込んだ．現在外来で経過観察中であるが，NSVTを含め心室性頻拍は認めず，抗不整脈薬を含めた内服加療は行っていない．

考察

これまでの疫学的調査から，有症候，無症候にかかわらずBrugada症候群はほとんどが男性例で30～50歳代にピークがあり，70歳以上の高齢者例の報告は少ないとされている[8]．今回，われわれが経験した2症例はいずれも，Brugada症候群の好発年齢よりは高年齢であったため，器質的心疾患の除外診断目

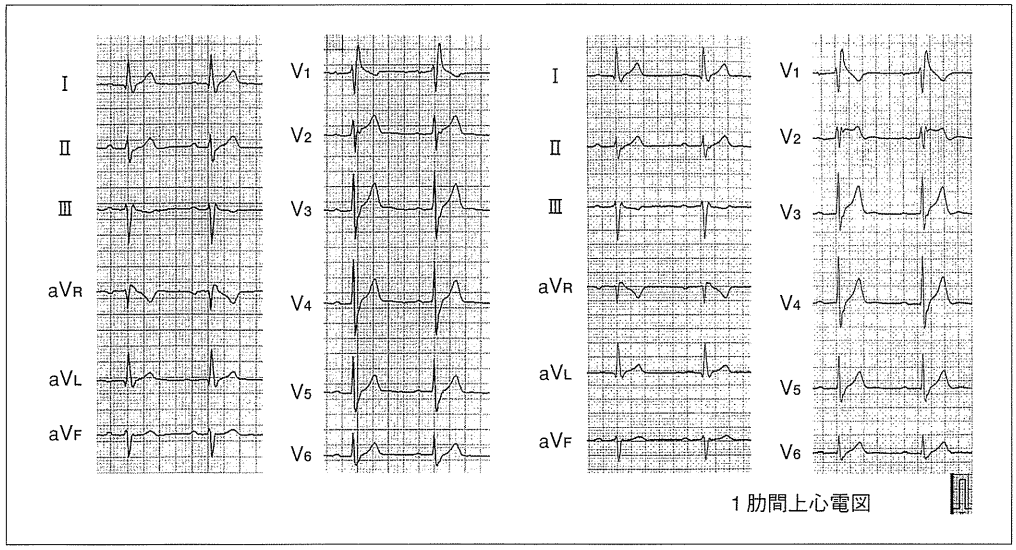

図4
症例2 入院時心電図所見
洞調律QRS幅160ms R-R間隔1,000ms，脈拍60/分V_2でsaddleback型のST上昇を認める．1肋間上では，V_2でST部分がcoved型への変化を認める．

的でCT検査を行ったところ，脂肪変性や瘤状の変化が認められ，画像診断上はARVCが疑われた．このため，Brugada型心電図所見を呈したARVC類縁疾患群であった可能性が示唆された．

今回の2症例に共通することは，心電図でBrugada型心電図を呈し，比較的高齢であり，EPSでVFが誘発されたことである．

通常，ARVCは心室性期外収縮や心室頻拍などの心室性不整脈が初発で，比較的初期では右室の形態異常が顕著ではないが，その後の精査で右室の拡張，収縮不全などの形態学的異常が認められ画像診断で診断されることもある．一般にARVCの特徴的心電図所見として，$V_{1\sim3}$誘導における右脚ブロック波形を伴わない110ms以上のQRS幅や右室の局所的な伝導遅延を示すε波があり[9]，これら伝導遅延を示す原因は右室において心筋細胞が脂肪や線維組織に置き換わることによるとされている[10]．しかし，ARVCはさまざまな心電図波形を示すことも報告されており，特徴的心電図所見であるε波も全例にみられるわけではなく47%の症例に認められる程度[11]である．そのため心電図単独での診断は困難であり，Brugada症候群との鑑別が問題となる場合がある．今回，われわれは施行しなかったが，Yodogawaら[12]はWavelet変換によるBrugada症候群とARVCの鑑別を周波数の違いから述べており鑑別に有用であった可能性がある．

また，EPSではBrugada症候群は有症候性群でVFの誘発が68～83%であり[13]，ARVCでは90%以上で心室頻拍(ventricular tachycardia；VT)が誘発される[14]とされている．今回の2例はEPSでVTではなくVFが誘発されたことを考慮することより電気的に不安定な病態が潜んでいた可能性がある．

ARVCの臨床上の確定診断には，画像診断を含め，心電図診断，家族歴などの総合診断が必要とされているが[15]，近年の遺伝子診断学の発展とともに遺伝子検査も補助診断になり得る可能性がある．今回の自験例では，いずれも遺伝子診断を施行していないが，Brugada症候群，ARVCそれぞれに特異的とされる遺伝子が発見されている．Brugada症候群では，およそ15～30%程度の患者に心筋Naチャネルの蛋白をコードする*SCN5A*遺伝子変異を認め[3]，ARVCでは約20～30%の症例に遺伝的背景を認め，その原因遺伝子としてplakoglobin，desmoplakin，plakophilin-2，desmogein-2，transforming growth factor-β_3，ryanodine receptor 2などが同定されている[9]．しかし，ARVCあるいはBrugada症候群のすべての症例において遺伝子異常が認められるわけではない．そこで簡易的に形態学的な異常をチェックする意味でもCT検査などは有用であると考えられる．現時点までで

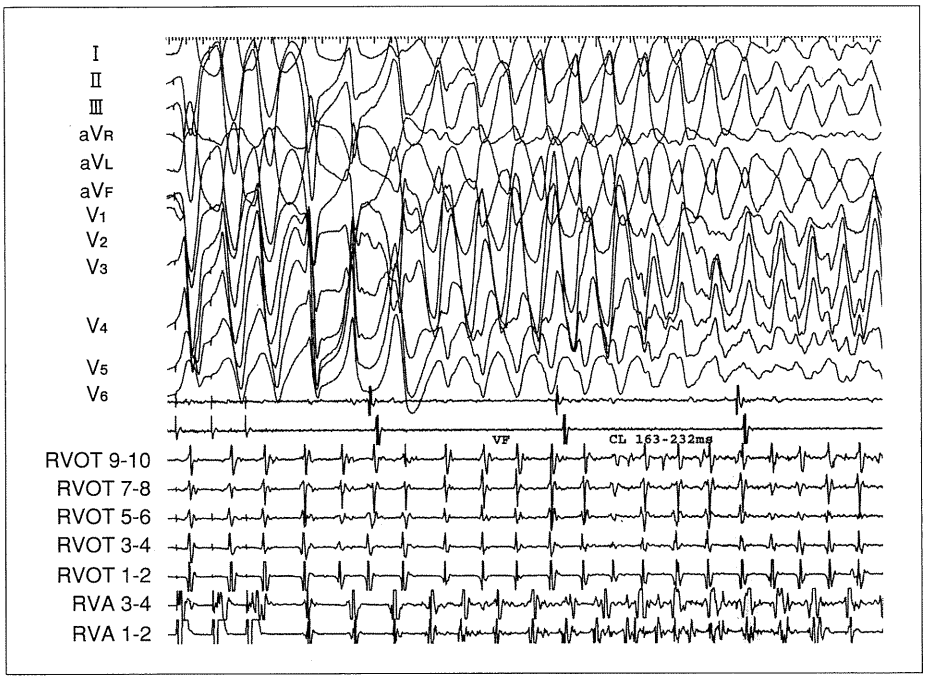

図 5
右室心尖部からの3連早期刺激(400/270/210/200ms)でVFが誘発された(薬剤負荷はなし)．誘発時は多形性心室頻拍を呈し，VFへ移行した．

表　自験例および過去に報告のあったBrugada型心電図所見を呈しARVCとの関連が示唆された症例

	年齢 性別	安静時 心電図所見	画像検査 (CT/MRI)	EPS所見	生検
症例 1	62歳，男性	$V_{1\sim3}$ ST上昇	造影CTで右室瘤・脂肪変性	VF誘発	未施行
症例 2	77歳，男性	右脚ブロック，V_2でST上昇	単純CTで右室に脂肪変性	VF誘発	未施行
Tadaら[7]	63歳，男性	右脚ブロック，$V_{1\sim3}$でST上昇	CTで右室心外膜にadipose tissue	未施行 ただしVF documentされている	脂肪組織あり
Izumiら[22]	73歳，男性	右脚ブロック，V_2でST上昇	MRIで右室拡張	VF誘発されず	心室中隔で脂肪組織の置換あり

症例1，2ともにCT上の構造学的変化および超音波心エコー法(ultrasonic echocardio graphy；UCG)での心機能低下は認めていないが，ARVCは進行性の疾患であることを考慮すると，今後も引き続き経過観察することが重要であると考えられた．

今回の自験例はいずれも，McKennaらが提唱しているARVCの診断基準は満たしていないが[16]，Brugada型心電図所見を呈するARVCが存在する可能性は以前から指摘されており[17]，小児例ではあるが，Brugada症候群に類似する臨床所見を呈したARVCの例なども報告されている[18]．つまり，今回の自験例はBrugada型心電図所見を呈するARVC類縁疾患であったと考えられる．

最近，Nademaneeらは，Brugada症候群によるVFのため，ICD頻回作動を認める症例で3D mapping systemを用いたところ，右室流出路(right ventricular outflow tract；RVOT)前壁の心外膜側に異常な遅延脱分極電位を認め，この部位でのアブレーションを行うことによりBrugada型心電図が正常化し，繰り返すVFエピソードを軽減できたことを報告してい

る[19]．また，ARVCのVTに対してもsubstrate-based ablationの有効性が報告されており，RVOT前壁側に異常低電位領域が多いとされている[20)21)]．以上のことを考慮すると，Brugada症候群もARVCもRVOT付近での異常電位出現がVT・VFの出現に関与しており，これが前胸部誘導での心電図波形異常につながっている可能性がある．

比較的高齢者でBrugada型心電図所見を呈した症例の特徴を表に示したが，いずれもCTをはじめとした画像検査が補助診断として用いられている[22]．

今後も，Brugada型心電図を示した症例の中で，Brugada症候群の好発年齢ではない高齢者の場合には本例のような疾患群が隠れている可能性もあるため，画像検査は積極的に施行すべきであると考えられた．

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Circulation Journal
Official Journal of the Japanese Circulation Society
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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Characteristics of Induced Ventricular Fibrillation Cycle Length in Symptomatic Brugada Syndrome Patients

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Background: Limited information is available on the ventricular fibrillation (VF) spectrum in Brugada syndrome (BS) patients. We clarified differences in the VF cycle length (CL) using fast-Fourier transformation (FFT) analysis in symptomatic and asymptomatic BS patients.

Methods and Results: VF was induced by pacing from the right ventricular (RV) apex and/or RV outflow tract (RVOT) for >8 s. A 4096-point FFT analysis of results from 28 male BS patients (51.1±13.7 years old) was performed. Dominant frequency (DF) from phases 1 (4 s) to 6 was obtained at 2-s intervals. The average DF from surface and intracardiac electrograms (ECG: DF_{ECG}; ICE: DF_{ICE}, respectively) was compared between symptomatic and asymptomatic patients. Symptomatic patients had a significantly shorter effective refractory period at a CL of 600 ms at the RVOT than asymptomatic patients. DF_{ECG} significantly increased with phase (5.64±0.32 Hz in phase 1 to 6.16±0.52 Hz in phase 6) and was significantly higher in symptomatic patients than in asymptomatic patients. DF_{ICE} had the same characteristics as DF_{ECG}.

Conclusions: Induced VF in BS patients can be characterized using FFT analysis. Our data support the hypothesis that symptomatic patients have a significantly shorter VF CL than asymptomatic patients. (*Circ J* 2012; **76:** 624–633)

Key Words: Brugada syndrome; Electrophysiological stimulation; Fast-Fourier transformation analysis; Ventricular fibrillation

Brugada syndrome (BS) associated with ventricular fibrillation (VF) is a specific electrocardiogram (ECG) abnormality of right bundle branch block with ST segment elevation in the right precordial leads.[1,2] BS patients have no apparent heart disease; therefore, ECG findings are the most useful parameters for diagnosing this genetic disease.[2]

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The clinical implication of electrophysiological study (EPS) for risk stratification in patients with ischemic heart disease and low left ventricular ejection fraction is relatively clear.[3] However, in BS patients, spontaneous VF depends primarily on trigger factors rather than substrate existence. In asymptomatic BS patients, although VF is often induced during electrophysiological tests, spontaneous VF incidence is very low.[4–6] Therefore, the use of EPS to further stratify intermediate-risk patients with Brugada-type ECG remains controversial.[4–7]

Symptomatic BS patients showed a relatively higher VF inducibility than asymptomatic patients;[8] therefore, some differences in the electrophysiological substrate exist between both groups. We hypothesized that the electrophysiological VF substrate in BS patients is related to VF induction, VF cycle length (CL), and changes subsequent to induction.

Fast-Fourier transformation (FFT) is used to analyze the VF CL[9–12] and atrial fibrillation (AF).[13–15] Spectral analysis is useful for characterizing induced and spontaneous VF CL.[9–12] VF organization correlates with the VF CL, except at the center of fragmented electrograms.[16] VF CL and its change should depend on the electrophysiological characteristics of each patient; however, little information is available regarding FFT analysis of ventricular ECGs during VF in BS patients.[17]

We hypothesized that symptomatic patients have a shorter VF CL (analyzed by FFT) than asymptomatic patients.

Received October 10, 2011; revised manuscript received November 21, 2011; accepted November 25, 2011; released online January 17, 2012 Time for primary review: 14 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-1144

Methods

Subjects

Between November 2003 and April 2011, we performed electrophysiological tests on 43 patients with Brugada-type or -like ECGs for risk stratification; 28 male patients (51.0±13.7 years) diagnosed with BS and with induced VF for >8 s simultaneously recorded from 2 right ventricular (RV) sites [RV apex, (RVA) and RV outflow tract (RVOT)] were included. ECGs were obtained for all patients, and all underwent the Na^+ channel-blocker challenge test, coronary angiography, and cardiac echocardiography during hospitalization.

BS was diagnosed on the basis of the following previous study recommendations:[18] type 1 ECG showing spontaneous VF or Na^+ channel-blocker challenge test in the standard right precordial leads (leads V_{1-3}) or 1 intercostal space above the standard right precordial leads and absence of factors such as ischemia, electrolyte disturbance, or hypothermia that may cause ST segment abnormalities.

Brugada-like ECGs were defined by 3 repolarization patterns that mimicked types 1, 2, and 3 according to the Heart Rhythm Society and the European Heart Rhythm Association[2] in the standard right precordial leads (leads V_{1-3}), but did not fulfill the Brugada-type ECG criteria.

Subjects were divided into the symptomatic group, which included patients with a documented history of potentially lethal ventricular tachycardia, VF or syncope, and the asymptomatic group, which included patients with no documented episodes of potentially lethal ventricular arrhythmias and/or syncope. One patient with a history of syncope was assigned to the asymptomatic group because he did not have an abnormal ECG during syncope documented after discharge from the hospital and was subsequently diagnosed with epilepsy.

ECGs were obtained for all patients. Careful attention was paid to any RV enlargement and/or wall motion abnormalities to exclude arrhythmogenic RV cardiomyopathy. All patients provided written informed consent and the study was approved by the Institutional Clinical Research and Ethics Committee.

Na^+ Channel-Blocker Challenge Test

The Na^+ channel-blocker challenge test was performed using pilsicainide, as described previously.[18] Briefly, 1 mg/kg of pilsicainide, a so-called pure Na^+ channel blocker, was administrated intravenously over a 10-min period with continuous ECG and non-invasive blood pressure monitoring. During drug administration, a 12-lead ECG was recorded, and then the standard right precordial leads (V_{1-3}) and 3 leads at 1 intercostal space above the standard right precordial leads were recorded (V_{4-6}). Drug administration was stopped immediately if ST elevation >0.5 mV, extensive QRS prolongation, unfavorable symptoms, and/or frequent ventricular arrhythmias were observed. The test was considered positive if the coved-type ECG pattern (type 1 ECG) appeared in more than 1 right precordial lead.

Electrophysiological Study

Electrophysiological study was conducted as described previously.[19] All patients were fasted and all antiarrhythmic agents were discontinued for at least 5 half-lives. An intravenous propofol infusion was used to induce general anesthesia.

Recordings A standard 6F decapolar catheter with 2-mm width electrodes and 2-mm inter-electrode spacing was introduced via the right femoral vein or left and/or right subclavian vein. The catheters were positioned in the high lateral right atrium, His bundle region, and coronary sinus, with distal and proximal electrode pairs at RVA and RVOT. The 12 surface ECG leads were filtered at 0.5–100 Hz and recorded simultaneously with an intracardiac ECG. Bipolar endocardial electrograms were recorded with a 30–150 Hz filter at a sampling interval of 1 KHz using a computerized electrophysiology recorder (CardioLab v51D, GE Medical Systems, USA).

Stimulation Protocol Programmed electrical stimulation was delivered at twice the diastolic threshold at a 2-ms pulse width (Fukuda Denshi, Japan). The stimulation protocol was as follows: programmed stimulation initially at a basic CL (BCL) of 600 ms and then at 400 ms from the RVA with 2 extra stimuli and a minimum coupling interval at 180 ms of S_2S_3. The same stimulation was performed from the RVOT and was followed by programmed stimulation of 3 extra stimuli with a minimum coupling interval at 200 ms of S_2S_3 and S_3S_4 and then rapid pacing down to a CL of 240 ms or a 2:1 ventricular response from the RVA. The same stimulation protocol was repeated from the RVOT. When VF was induced during the pacing protocol, cardioversion was initiated after several seconds of observation to confirm the absence of spontaneous termination. A direct current (DC) was discharged after the appropriate delivery energy was reached. Stimulation was restarted 5 min after successful cardioversion, which occurred in all cases of induced VF. Cardioversion was not performed for 1 VF episode because of spontaneous termination at 15.8 s immediately before DC discharge.

VF was defined as a fast irregular ventricular rhythm with continuously changing morphology and a CL <200 ms.[20] VF duration was calculated from the last stimulation to the last VF beat. The mean VF duration was 14.6 s (range 8.7–19.2 s).

Signal Processing and FFT Analysis Data were analyzed using methods described previously.[13] The VF episode was selected on the CardioLab screen and then transferred to a hard disk. Binary data from the ventricular ECG was retrieved from the hard disk of the CardioLab system and transformed into compatible data for multipurpose physio-informatic analysis with BIMUTAS II for Windows (Kissei Comtec, Ltd, Tokyo, Japan). A total of 6 phases of 4-s data were selected as an epoch (**Figure 1**). Surface ECGs (leads I, aV_F, V_1, and V_5) and rectified bipolar electrograms (RVOT distal pair: RVOTd; RVOT proximal pair: RVOTp; RVA distal pair: RVAd; RVA proximal pair: RVAp) were analyzed by 4096-point FFT (spectral resolution: 0.24 Hz) with a Hamming window using BIMUTAS II, as previously reported.[13] Each of the 4 surface ECGs in each epoch was padded to 4,096 points with zeros. Data >2 s from the last phase in 4 patients were created to 4,096 points with zero padding for FFT analysis.

The power spectrum of electrograms at each recording site was obtained, and the dominant frequency (DF),[11,14] defined as the frequency of the peak with the largest amplitude, was obtained from each epoch in each phase. We assessed the DF from surface ECGs and bipolar electrograms. In 1 patient, data from the ECG (lead V_5) were abandoned because of the poor recording.

Average DFs from the surface ECGs and intracardiac electrograms (ICEs) were calculated for quantitative comparisons and termed the DF from surface ECG (DF_{ECG}) and DF from ICE (DF_{ICE}) in each phase (**Figures 1,2**). The effective refractory period (ERP) was defined as the maximum coupling interval during a single program stimulation that failed to produce a reaction in the ventricle.

Statistical Analysis

Data are presented as the mean±standard deviation (SD). A simple regression test was used to compare 2 data points.

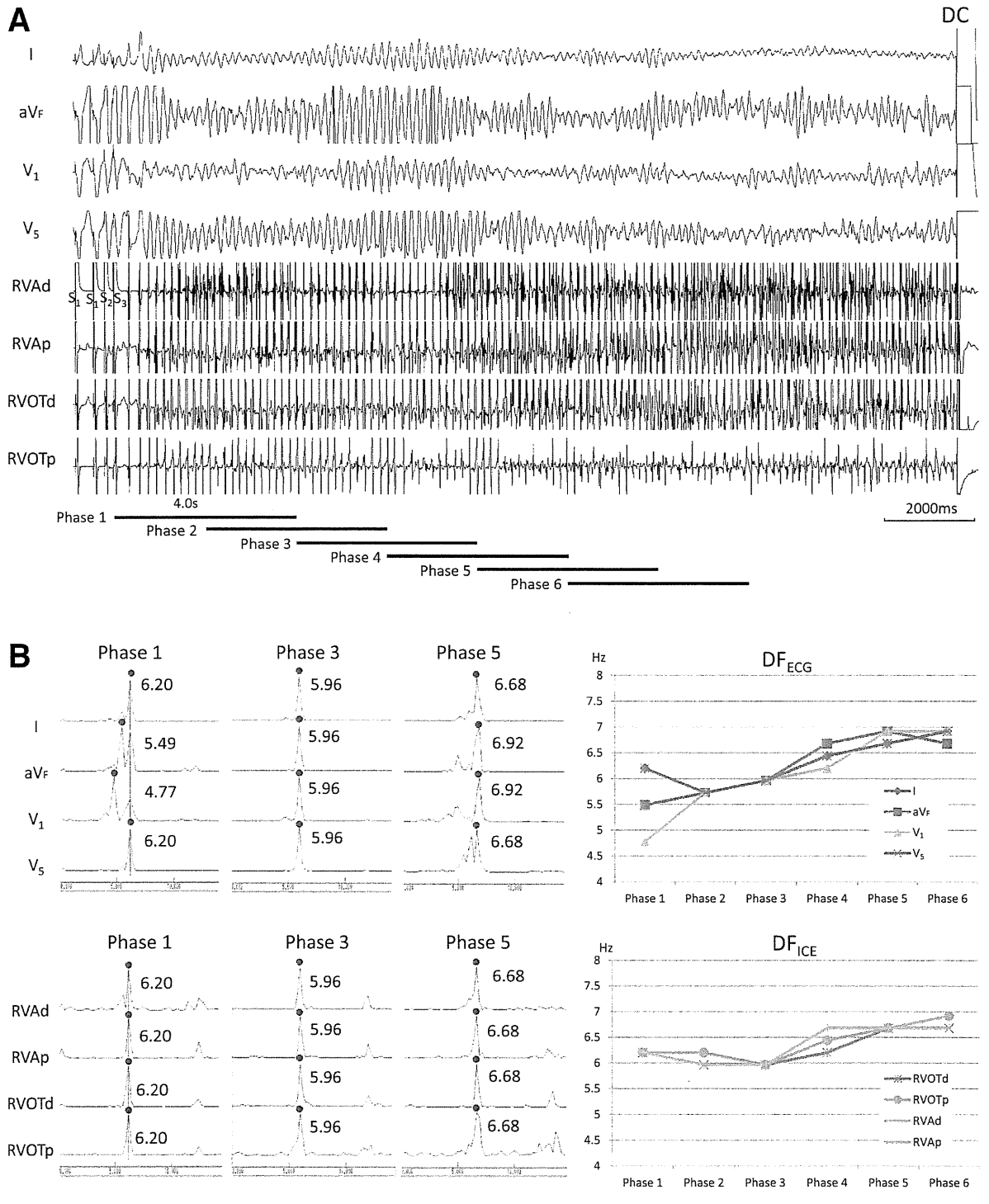

Figure 1. Representative case of induced ventricular fibrillation (VF) in a symptomatic Brugada syndrome patient. (**A**) Surface electrocardiograms (ECGs) and intracardiac electrograms from a 63-year-old man referred for further examination because of a history of syncope and Brugada-type ECG. VF was induced by ventricular stimulation in double mode ($S_1/S_2/S_3$=400/240/200 ms) from the right ventricular apex (RVA) and right ventricular outflow tract (RVOT). (**B**) Fast-Fourier transformation (FFT) analysis. (**Left**) Raw data of FFT analysis in phases 1, 3, and 5. The dominant frequencies (DF_{ECG} and DF_{ICE}) are indicated as the number and dot at the maximum power spectrum. (**Right**) DF_{ECG} change with phase (1–6) is depicted in the upper panel and DF_{ICE} change with phase in the lower panel. DF_{ECG} and DF_{ICE} gradually increase with phase. ICE, intracardiac electrogram; RVAd, RVA distal pair; RVAp, RVA proximal pair; RVOTd, RVOT distal pair; RVOTp, RVOT proximal pair. Phase number indicates a 4-s data segment.

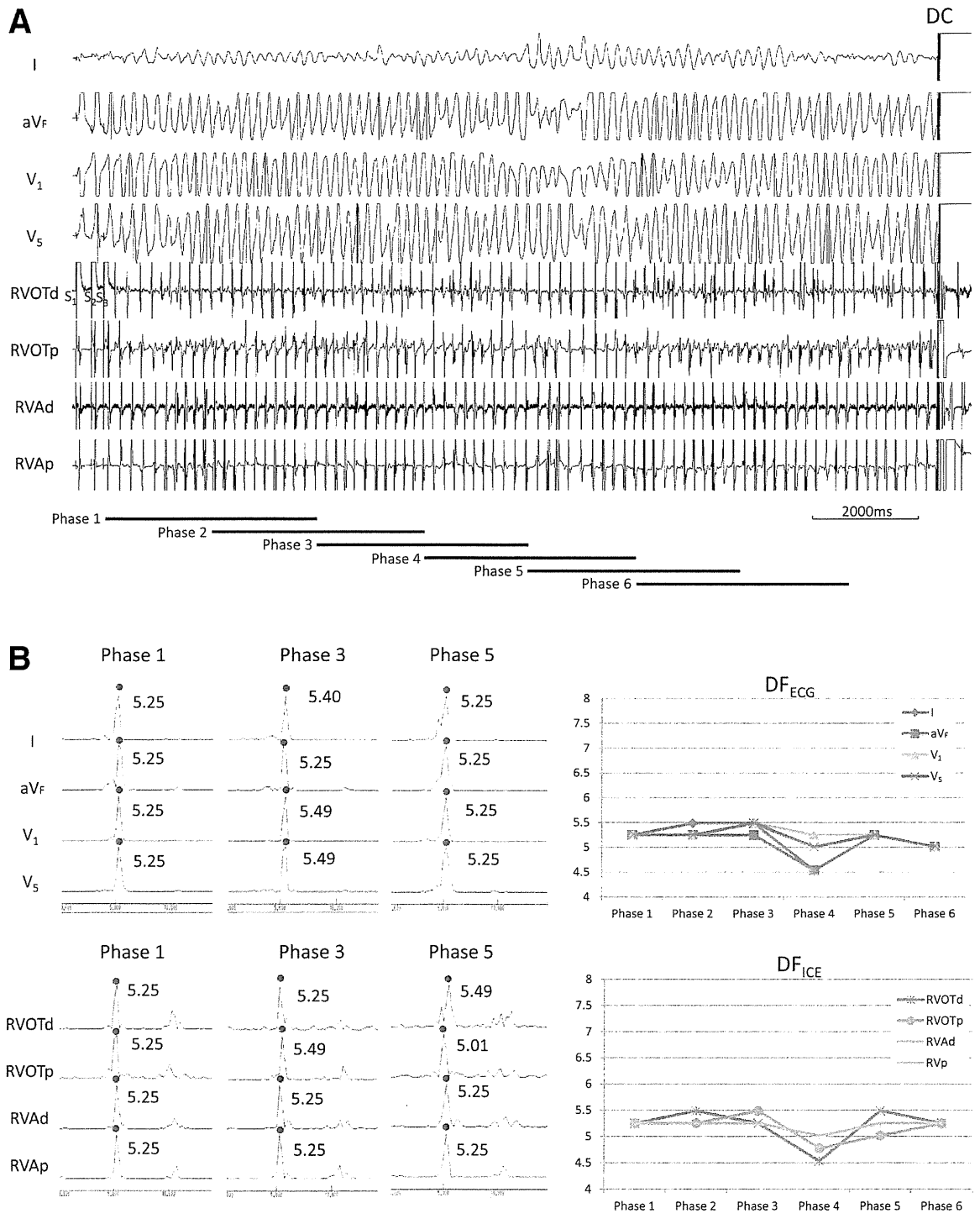

Figure 2. Representative case of induced ventricular fibrillation (VF) in an asymptomatic Brugada syndrome patient. (**A**) Surface electrocardiograms (ECGs) and intracardiac electrograms (ICE) from a 26-year-old man with asymptomatic Brugada syndrome referred for further examination of a Brugada-like ECG after a regular check-up. VF was induced by ventricular stimulation in double mode ($S_1/S_2/S_3$=600/290/230 ms) from the right ventricular outflow tract (RVOT). (**B**) Fast-Fourier transformation (FFT) analysis. (**Left**) Raw data of FFT analysis in phases 1, 3, and 5. The dominant frequencies (DF_{ECG} and DF_{ICE}) are indicated as the number and dot at the maximum power spectrum (**Right**) DF_{ECG} change with phase (1–6) is depicted in the upper panel and DF_{ICE} change with phase in the lower panel. DF_{ECG} and DF_{ICE} did not change significantly with phase RVAd, RVA distal pair; RVAp, RVA proximal pair; RVOTd, RVOT distal pair; RVOTp, RVOT proximal pair. Phase number indicates a 4-s data segment.

Table 1. Clinical Characteristics of the Patients With Brugada Syndrome

	Asymptomatic	Symptomatic	Total	P
n	13	15 (3)*	28	
Male	13	15	28	
Family history	4	2	6	0.262
ICD implantation	3	12	15	0.003
Age (years)	49.4±13.4	52.6±14.2	51.1±14	0.545
ERP				
RVA BCL 600 (ms)	238±14	237±16	238±15	0.847
RVA BCL 400 (ms)	218±12	216±14	217±13	0.734
RVOT BCL 600 (ms)	238±9	229±12	234±11	0.030
RVOT BCL 400 (ms)	223±16	218±18	220±17	0.444
Pacing site induced VF1	RVA 3, RVOT 10	RVA 5, RVOT 10	RVA 8, RVOT 20	0.547
Mode of induction VF1	Double 6, Triple 7	Double 9, Triple 6	Double 15, Triple 13	0.463
Duration of VF1 (s)	14.9±2.5	14.3±1.8	14.6±2.1	0.510
Mode of termination	Spontaneous† 1, DC 12	Spontaneous 0, DC 15	Spontaneous 1, DC 27	0.942

*Documented ventricular fibrillation, †induced ventricular fibrillation terminated spontaneously at 15.8 s after the last stimulation (S_3).
P, asymptomatic group vs. symptomatic group; ICD, implantable cardioverter defibrillator; ERP, effective refractory period; RVA, right ventricular apex; BCL, basic cycle length; RVOT, right ventricular outflow tract; VF1, ventricular fibrillation induced first; DC, direct current.

One-way analysis of variance (ANOVA) was used for phase changes. Repeated measures ANOVA was used to detect differences in phase changes between both groups. The chi-square test for independence was used for comparison of prevalence. Student's t-test (unpaired or paired) was used when appropriate. Analyses were performed using StatView 5.0 software for Windows (SAS Institute Inc, Cary, NC, USA).

Results

Clinical Characteristics of BS Subjects

Subjects were 28 male BS patients aged 51.1±14 years. No significant difference in age was observed between the 2 groups. Implantable cardioverter defibrillators (ICDs) were implanted in 3 asymptomatic and 12 symptomatic patients during hospitalization (Table 1).

Electrophysiological Findings

Symptomatic patients had significantly (P=0.03) shorter ERP at a BCL of 600 ms at the RVOT than asymptomatic patients (Table 1), although no significant differences were observed for ERP at a BCL of 400 ms at the RVOT or at 600 and 400 ms at the RVA between groups (Table 1). VF was induced by pacing from the RVOT in 20 patients and from the RVA in 8 patients. However, no significant differences between both groups were observed regarding pacing site, mode or duration of induced VF (Table 1). VF induced from the RVOT (BCL 600 ms/S_1 270/S_2 200 ms/S_3 200 ms) in 1 asymptomatic patient terminated spontaneously at 15.8 s after the last stimulation (S_3).

Representative Cases of Induced VF

A 63-year-old man with symptomatic BS (Figure 1) was referred to our department for further examination because of a history of syncope and Brugada-type ECG (Figure 1A). VF was induced by ventricular stimulation in double mode from the RVA. Figure 1B shows the FFT power spectrums of phases 1, 3, and 5: DF_{ECG} in leads I, aV_F, V_1, and V_5 gradually increased with the phase. DF_{ICE} in the RVAp, RVAd, RVOTd, and RVOTp revealed the same characteristics as DF_{ECG} (Figure 1B).

A 26-year-old man with asymptomatic BS (Figure 2) was referred to our department for further examination of a Brugada-like ECG after a regular check-up. VF was induced by ventricular stimulation in double mode ($S_1/S_2/S_3$=600/290/230 ms) from the RVOT. VF morphology appeared to be more organized compared with the symptomatic case. Figure 2B shows the raw FFT power spectrums of phases 1, 3, and 5. Unlike the previously described patient, DF_{ECG} did not change much with phase. DF_{ICE} in the RVAp, RVAd, RVOTd, and RVOTp showed the same characteristics as DF_{ECG} (Figure 2B).

Relationship Between DF_{ICE} and DF_{ECG}

DF_{ICE} and DF_{ECG} showed a significant relationship in phases 1 (r=0.820, P<0.0001), 2 (r=0.788, P<0.0001), 3 (r=0.881, P<0.0001), 4 (r=0.924, P<0.0001), 5 (r=0.883, P<0.0001), and 6 (r=0.929, P<0.0001) (Figure 3). Significant differences between DF_{ICE} and DF_{ECG} in each phase were absent (Table 2).

Relationship of DF Between RVAd and RVOTd

DF between RVAd and RVOTd showed a significant relationship in phases 1 (r=0.651, P=0.0002), 2 (r=0.788, P<0.0001), 3 (r=0.639, P=0.0003), 4 (r=0.770, P<0.0001), 5 (r=0.757, P<0.0001), and 6 (r=0.699, P<0.0001) (Figure 3). Significant differences in DF were not observed between RVAd and RVOTd in any phase (RVA vs. RVOT, 5.70±0.43 vs. 5.77±0.44 Hz in phase 1, 5.98±0.40 vs. 5.95±0.41 Hz in phase 2, 6.13±0.40 vs. 6.02±0.47 Hz in phase 3, 6.08±0.58 vs. 6.01±0.66 Hz in phase 4, 6.15±0.53 vs. 6.17±0.57 Hz in phase 5, and 6.26±0.53 vs. 6.15±0.54 Hz in phase 6).

DF_{ECG} and DF_{ICE} Reproducibility

A second induced VF in a control state was recorded in 17 of the 28 patients. No significant relationship was observed for DF_{ECG} in phases 1–3 (initial phase) between the first and second VF episodes. However, a significant relationship was observed for DF_{ECG} in phases 4 (r=0.543, P=0.024), 5 (r=0.700, P=0.0018), and 6 (r=0.555, P=0.032) (Figure 4) between the first and second VF episodes; thus, reproducibility was observed in phases 4–6 (late phase). On the other hand, no sig-

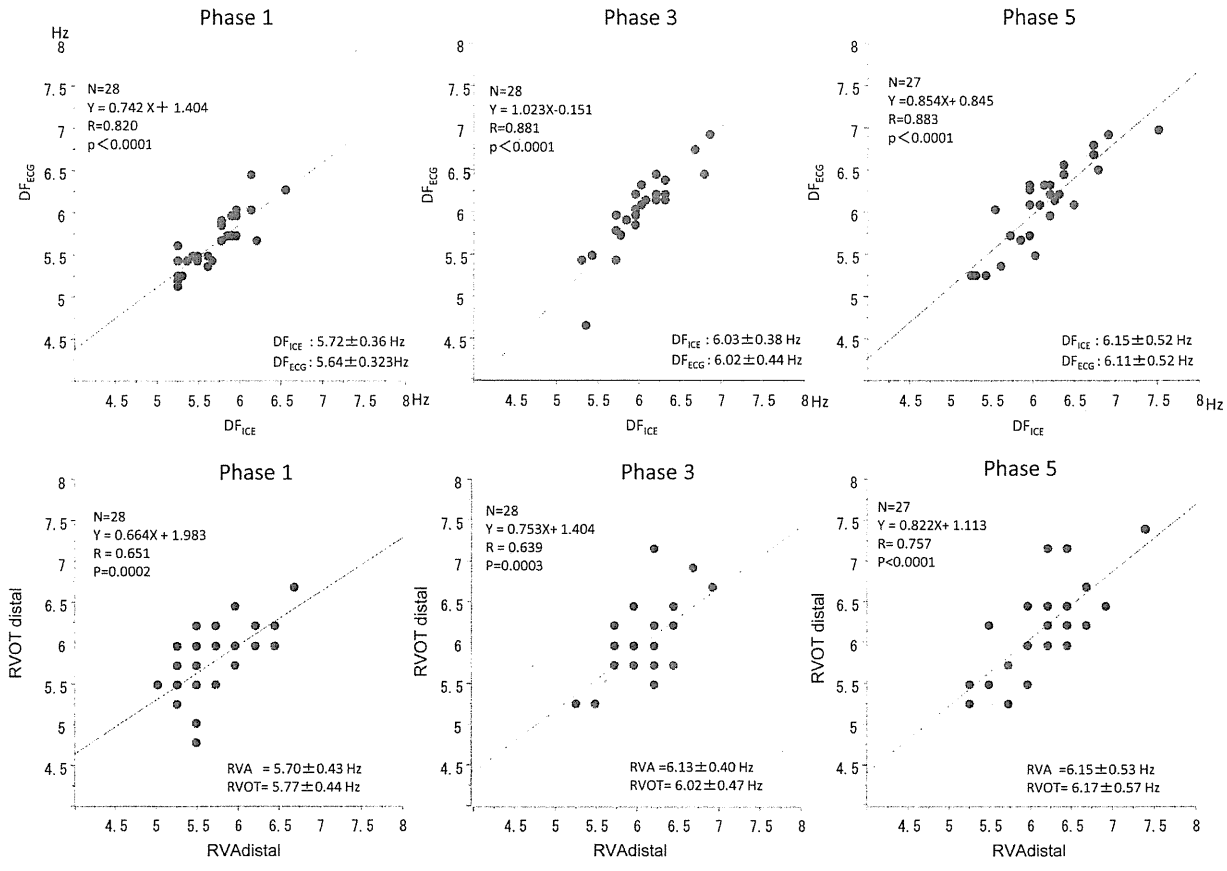

Figure 3. Relationship between dominant frequency (DF) from surface electrocardiograms (DF_{ECG}) and intracardiac electrograms (DF_{ICE}) and relationship of DF between the right ventricular apex (RVA) and RV outflow tract (RVOT) distal pairs. DF_{ECG} and DF_{ICE} show a significant relationship in phases 1, 3, and 5 (**Upper**). DF between RVA and RVOT distal pairs shows a significant relationship in phases 1, 3, and 5 (**Lower**). RVAd, RVA distal pair; RVAp, RVA proximal pair; RVOTd, RVOT distal pair; RVOTp, RVOT proximal pair.

Table 2. Transition of DF With Phase

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6	P
All subjects (n)	28	28	28	28	27	26	
DF_{ECG} (Hz)	5.64±0.32	5.77±0.45	6.02±0.44	6.07±0.58	6.11±0.52	6.16±0.52	0.0003#
DF_{ICE} (Hz)	5.72±0.36	5.92±0.38	6.03±0.38	6.06±0.59	6.15±0.52	6.19±0.49	0.002#
P$	0.399	0.192	0.943	0.959	0.764	0.854	
DF_{ECG}							
Asymptomatic (Hz)	5.55±0.27	5.60±0.42	5.80±0.47	5.79±0.60	5.93±0.48	6.01±0.48	0.022*
Symptomatic (Hz)	5.73±0.35	5.94±0.42	6.21±0.33	6.30±0.46	6.23±0.50	6.27±0.53	
P$	0.148	0.043	0.011	0.017	0.123	0.211	
DF_{ICE}							
Asymptomatic (Hz)	5.57±0.33	5.73±0.28	5.84±0.34	5.80±0.67	5.90±0.44	6.00±0.44	0.012*
Symptomatic (Hz)	5.84±0.34	6.08±0.39	6.20±0.34	6.28±0.35	6.34±0.50	6.35±0.48	
P$	0.042	0.015	0.009	0.027	0.026	0.064	

#One-way ANOVA, *repeated measure ANOVA, $unpaired t-test.
DF, dominant frequency; P, asymptomatic group vs. symptomatic group; DFECG, dominant frequency from surface ECG.

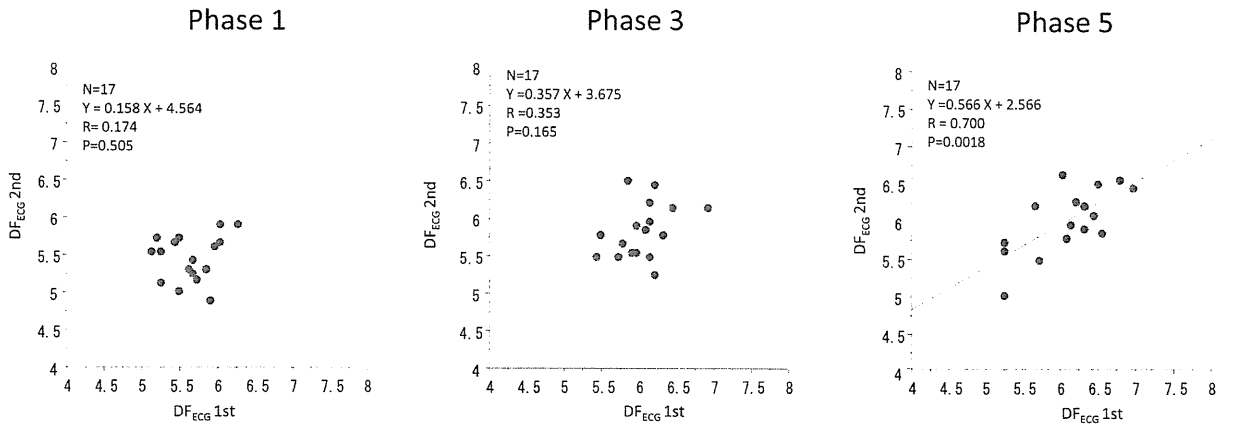

Figure 4. Dominant frequency (DF_{ECG}) reproducibility. A significant relationship is observed for DF_{ECG} between the first (X axis) and second ventricular fibrillation (Y axis) episodes in phase 5.

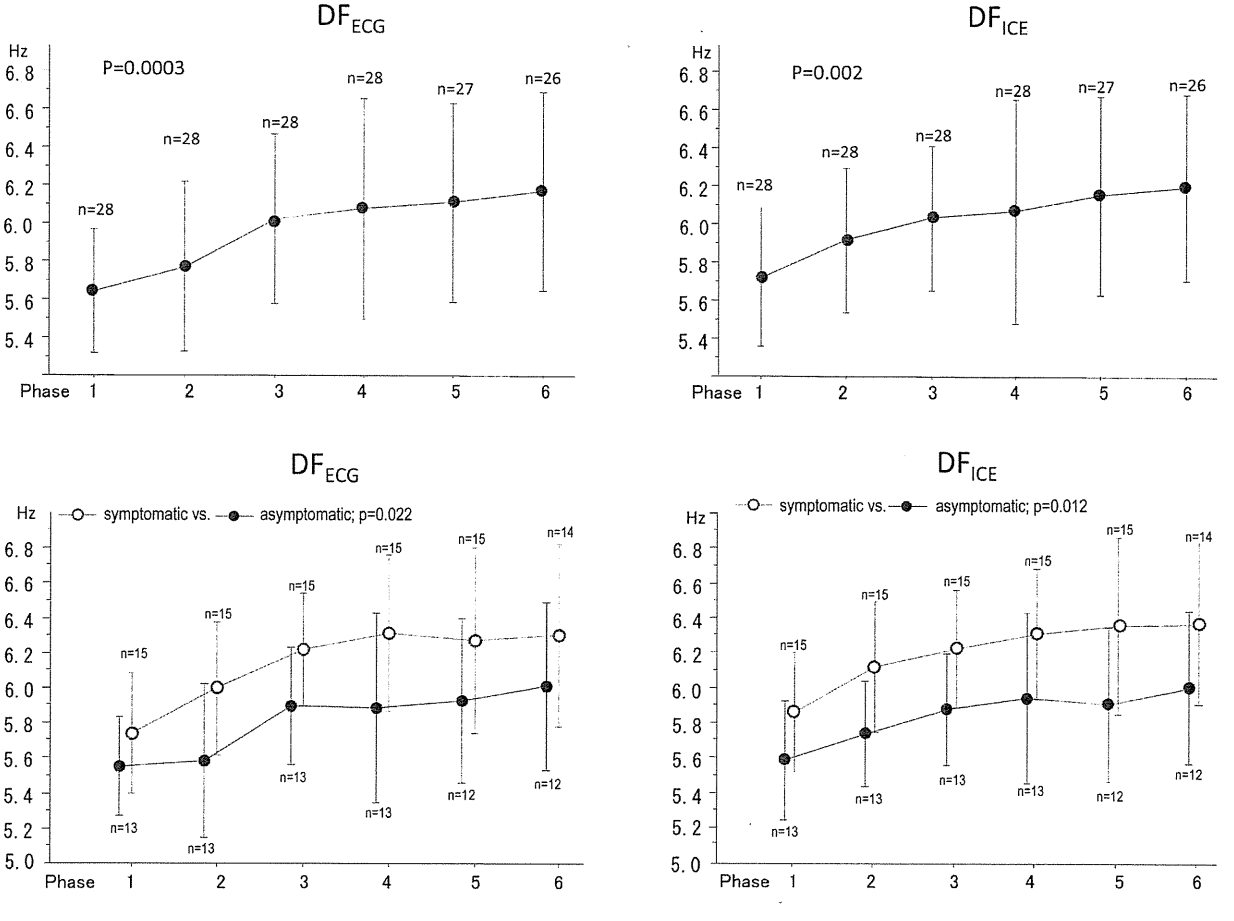

Figure 5. Transition of dominant frequency (DF_{ECG} and DF_{ICG}) with phase. (**Left**) DF_{ECG} change for all patients (**Upper**) and symptomatic and asymptomatic groups (**Lower**). (**Right**) DF_{ICE} change for all patients (**Upper**) and symptomatic and asymptomatic groups (**Lower**).

nificant relationship was observed for DF_{ICE} in phases 1 and 2 (initial phase) between the first and second VF episodes, which was similar to DF_{ECG}. A significant relationship was observed for DF_{ICE} in phases 3 (r=0.633, P=0.0064), 4 (r=0.620, P=0.008), 5 (r=0.625, P=0073), and 6 (r=0.739, P=0.002) between the first and second VF episodes.

Transition of DF_{ECG} and DF_{ICE} With Phase (Figure 5)

DF_{ECG} significantly (P=0.0003) increased from phase 1 to 6 (5.64±0.32 Hz to 6.16±0.52 Hz). In the comparison of DF and phase between both groups, symptomatic patients had significantly higher (P=0.022) DF_{ECG} with phase than asymptomatic patients according to repeated ANOVA. DF_{ECG} in each group was significantly high in phases 2–4 (**Table 2**).

DF_{ICE} significantly (P=0.002) increased from phases 1 to 6 (5.72±0.36 Hz to 6.19±0.49 Hz). In the comparison of DF and phase between both groups, symptomatic patients had significantly higher (P=0.012) DF_{ICE} with phase than asymptomatic patients according to repeated ANOVA. DF_{ICE} in each group was significantly high in phases 1–5 (**Table 2**).

Follow-up Study

ICDs were implanted in 12 symptomatic patients and 3 asymptomatic patients (**Table 1**). Appropriate shocks were delivered in only 2 symptomatic patients during the average observation period of 41±27 months.

Discussion

We determined a relatively shorter ERP at the RVOT and higher DF_{ECG} in symptomatic patients. These patients have a different electrophysiological substrate than asymptomatic patients. More of the symptomatic patients had an ICD implanted than the asymptomatic patients.

We diagnosed BS as described previously[2] using additional right precordial leads located 1 intercostal space above the standard right precordial leads (V_{1-3}) because some patients showed type 1 ECG only with additional leads, even if normal ECGs were seen with standard leads (V_{1-3}).[18] A Na^+ channel-blocker challenge test using pilsicainide was performed to unmask intermittent or concealed Brugada-type ECGs. There is still controversy regarding the specificity of these drugs for BS; therefore, only type 1 ECG was regarded as a Brugada-type ECG after the Na^+ channel-blocker challenge test to avoid overestimating BS.

EPS for Risk Stratification in BS

Symptomatic patients had relatively higher VF inducibility than asymptomatic patients.[8] EPS is the primary method used for risk stratification in BS; however, a meta-analysis conducted in 2006 showed that EPS is of little value for predicting spontaneous VF.[21] In BS patients, spontaneous VF depends primarily on trigger factors rather than substrate existence. VF inducibility in asymptomatic patients varies, but is not that low at 37%[5]–57%.[4] In contrast, spontaneous VF during follow-up is very low, 0.5% per year,[4,5] compared with that predicted on the basis of a report by Brugada et al.[7] Using 95% confidence limits, the risk for spontaneous VF at 4–5 years of follow-up is probably between 1% and 6% for asymptomatic patients with inducible VF, and between 1% and 4% for those with negative EPS results.[22] Therefore, the use of EPS to stratify intermediate risk in Brugada patients remains controversial.[22] These EPS assessments were included only if VF was induced and not VF CL or a change in CL.

RVOT Electrophysiological Characteristics

The induction of VF suggests the existence of a VF electrophysiological substrate. Several studies have indicated that the RVOT is probably the site of electrophysiological substrate in BS patients.[23–25]

In the present study, VF inducibility by pacing from the RVOT was higher than that from the RVA (71% vs. 29%), which concurred with a previous study (59% vs. 27%).[26] Abnormally low voltage, prolonged duration, and fractionated late potentials have been observed in the anterior aspect of the RVOT epicardium, but not in the endocardium.[24] This finding may be explained by abnormal repolarization at the RVOT.[27] Symptomatic patients had a significantly shorter ERP at a CL of 600 ms at the RVOT than asymptomatic patients (**Table 1**), consistent with previous studies that identified a shorter ERP as one of the electrophysiological substrates of AF or VF. We hypothesized that the DF at the RVOT was higher than that at the RVA. The DF between RVAd and RVOTd showed a significant relationship in all phases, and the DF at the RVOT was similar to that at the RVA. The findings did not support our hypothesis. The major reason for this discrepancy is that bipolar electrograms at the ventricular endocardium cannot gain the information of ventricular electrograms at the epicardial site of the RVOT.[23,24] An epicardial recording during VF is required to prove our hypothesis.

FFT Analysis of ECGs and ICEs

Surface ECGs were analyzed without signal processing because the shape of the waves is similar to that of sine waves. A similar DF was observed in 2 or 3 leads in all except 5% of the epochs analyzed in surface ECGs of human VF.[12] We selected ECG leads I, aV_F, V_1, and V_5 because they represent the direction of the ventricular electrical vector. A similar DF was observed in ECG leads I, aV_F, V_1, and V_5 in this study. Average DF of 4 surface ECGs and intracardiac recording sites were assigned as DF_{ECG} and DF_{ICE} for quantitative comparison. We used DF_{ECG} and DF_{ICE} obtained from 4-s data in each phase to compare VF CL, because VF CL is known to change and increase with time.[11,12] Because VF duration was limited and different in each patient, we compared the DF_{ECG} and DF_{ICE} maximum of phase 6. Data for 1 patient at phase 5 and 2 patients at phase 6 were absent.

The characteristics of the electrical signals during VF in humans have been analyzed in several studies[9–12,20] regarding heart disease[28] or drugs.[11] The initial phase DF was 8–12 Hz in dogs and somewhat lower in humans.[11] In previous FFT analysis of surface ECGs, the mean VF duration was 21 s (range 11–34 s).[12] In this study, 28 BS patients had VF induced for >8 s recorded from 2 RV sites. The mean VF duration was 14.6 s.

During VF, myocardial cells are re-excited as soon as their refractory period ends.[29] Transmembrane potential recordings demonstrate that there is no diastolic interval between successive action potentials, and that there is only a small difference in the ERP during VF. Therefore, cells are re-excited as soon as they have regained excitability.[29]

DF Reproducibility

It is well known that the mean VF interval determined by FFT analysis correlates well with the ventricular refractory period by the extra stimulus technique.[30] The local refractory period influences VF dynamics by limiting the range of VF frequency.[31] The DF of short intervals of induced VF is highly reproducible.[32] However, frequency characteristics of repeated VF episodes induced in the same subjects revealed fair-to-

good, but not excellent reproducibility in patients undergoing ICD procedures.[10]

DF_{ECG} and DF_{ICE} showed a significant relationship, as previously reported.[33] Fibrillation recorded from the cardiac endocardium initially showed a DF similar to that recorded using body surface ECG.[33] After 3.3 min the frequency fell in lead II, but remained high in the endocardium.[33] Thus, the close relationship between DF_{ECG} and DF_{ICE} is maintained at least during the initial phase of induced VF (<3 min). However, in the present study, DF_{ECG} or DF_{ICE} reproducibility occurred after phase 3 or 4. DF reproducibility in phases 1 and 2 is not shown. These results indicate that time (phase) is important to achieve reproducible VF.

DF Change With Time or Phase

Human VF induced during EPS has a clear DF of activation and appears regularly in intracardiac recordings. Rate and stability increase during the initial VF phase.[11,12] In the present study, DF_{ECG} significantly increased with phase, which was consistent with previous studies.[11,12]

The rate of VF induced by 50 Hz alternate current increased rapidly during the first 5 s (4.1±0.8 Hz to 5.2±0.8 Hz), but only gradually thereafter.[12] DF_{ECG} of the first 3 s of unipolar ICEs during induced VF in 12 patients with ICDs and a primary history of ischemic heart disease (10 patients) was 4.75±0.57 Hz.[9] In another study, DF_{ECG} of the first 3 s of VF in 24 patients with ICDs and a primary history of ischemic heart disease (18 patients) was 5.1±1.1 Hz.[10] In the present study, DF_{ECG} of the initial phase in BS was 5.64±0.32 Hz, which was higher than in previous studies.[9,10] This finding may indicate that BS patients have a higher DF of the first VF phase than patients with apparent heart disease. The SD of the DF in this study was small, probably because of the single disease category.

Transition of DF Between Symptomatic and Asymptomatic Groups

We compared the DF change with phase between the symptomatic and asymptomatic groups. Symptomatic patients had a significantly higher DF_{ECG} with phase than asymptomatic patients (P=0.022). DF_{ICE} had frequency characteristics similar to DF_{ECG}.

Our data provide support for the hypothesis that symptomatic patients showed significantly shorter VF CL than asymptomatic patients. In this study, DF_{ECG} reproducibility occurred after phase 4. These results indicate that spectral analysis after 6 s from the last stimulus of induced VF may be useful as a risk stratification criterion for BS. However, long-term follow-up data is needed to prove this hypothesis.

Study Limitations

First, sample size in each group was relatively small. Second, a long observation time after EPS was not analyzed because of infrequent cardiac events. Third, although comprehensive genetic screening of all patients may have been ideal, it was not performed because it is costly and has an uncertain outcome. Fourth, clinical and induced VF episodes in humans may have different spectral characteristics;[9] however, the change in DF from induced VF should be indicated by the substrate of VF and the electrophysiological characteristics in BS patients. Fifth, long-term follow-up data are needed to prove whether a higher DF of induced VF is useful for risk stratification of BS patients. Sixth, because every symptomatic patient was asymptomatic before the first spontaneous episode, asymptomatic patients may have the same arrhythmic substrate as symptomatic patients. Thus, a different triggering mechanism may modify the induced VF frequency characteristics and may be responsible for the different clinical aspects of symptomatic and asymptomatic patients.

Conclusions

We found that symptomatic BS patients had a shorter ERP and higher DF at the RVOT than asymptomatic patients. Symptomatic patients had a significantly higher DF with phase than asymptomatic patients. ICEs had the same frequency characteristics as surface ECGs. Thus, we determined that it is feasible to characterize induced VF in BS patients using FFT analysis.

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