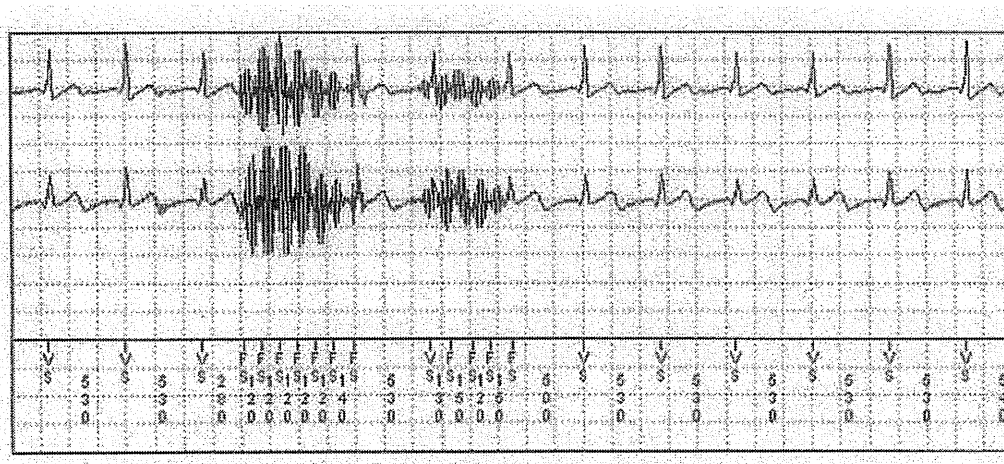

図9　電磁干渉（EMI）の心内心電図
Noiseが混入し，ICDがVFと認識（FS）していることがわかる．

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内科

Q 早期再分極症候群の最新トピック

早期再分極症候群（Brugada症候群以外）の最新トピックと，現時点での臨床現場での対処法について．

（長崎県　N）

A Brugada症候群と類似した臨床所見を持つものが多いが，現時点ではJ波を再現させる方法が定まっていないため，失神などの有症状例でJ波の存在を見逃さないことが重要である

早期再分極は健常人によく認められる心電図所見で，一般に良性であるとされる．近年，下壁，側壁誘導に明確なJ波を示す早期再分極症候群が心室細動（ventricular fibrillation；VF）発生に密接に関わり合っていることが報告され，さらにBrugada症候群との間に臨床上様々な類似点が認められることから，最近ではこれらをまとめて「J-wave症候群」と命名し，早期再分極症候群をサブタイプに分類することが提唱されている．

現時点では無症候例に対する定まった対処法はないが，症候例ではBrugada症候群の治療に準じて植込み型除細動器（implantable cardioverter defibrillator；ICD）の植込みが唯一の治療法である．

早期再分極とJ波

早期再分極パターンは，健常者や若年アスリートによく見られる心電図として古くから知られており，J点（すなわちQRSからSTに至る部分）の上昇として，心電図QRS下行脚のスラーあるいはノッチを認めるものと定義されている．古くから早期再分極パターンを認める症例でVFを来すものがあることは報告されており，我が国ではAizawaらが初めて報告している．

2008年にHaïssaguerreら[1]によってVFを伴う早期再分極症例がまとめられ，Brugada症候群，QT延長症候群，QT短縮症候群を除いた特発性VF，206例のうち31％で下壁または側壁誘導に0.1mV以上のJ点上昇を認める（健常群では5％）ことが報告された．さらに，これらの臨床的背景がBrugada症候群のそれに類似している点も報告している[1]．

こうした結果は，J波の成因はBrugada症候群のそれときわめて類似していることも示唆させるが，健常者でも多く認められる所見であること，Naチャネル遮断薬で変化しない症例も存在することから，同一かどうかについてはまだ結論が出ていない．

この早期再分極（J点の上昇）は，健常者に認められることが多い心電図であるが，Rossoら[2]は，早期再分極の特発性VFを来した患者45名と健常者，若年アスリートを比較した．その結果，特発性VFでは，0.1mV以上のJ点上昇が重要であり，さらに$V_{4\sim6}$の心電図変化は診断価値が低く，下壁誘導あるいはI，$_{a}V_{L}$誘導でのJ点上昇に注目すべきであると報告している．

現在では0.1mVのJ点上昇を隣接2誘導以上に認める場合を早期再分極症候群あるいはJ-wave症候群と呼んでいることが多いが，論文によっては0.2mVとしているものもあ

表1　早期再分極症候群（ERS, J-wave症候群）の分類

Type		遺伝性				後天性	
		ERS type 1	ERS type 2	ERS type 3	Brugada syndrome	虚血	低体温
電気的異常の局在		左室前側壁	左室下壁	左室，右室	右室	左室，右室	左室，右室
J-wave	局在	Ⅰ，V_4～V_6	Ⅱ，Ⅲ，aV_F	広範囲	V_1～V_3	いずれか	いずれか
	徐脈	増大	増大	増大	増大	N/A	N/A
	Na channel 遮断薬	変化小/不変	変化小/不変	変化小/不変	増大	N/A	N/A
性差		男性	男性	男性	男性	男性	男性，女性
VFとの関連		稀，健常男性ないし運動家	あり	あり，storm	あり	あり	あり
薬剤	quinidine	J点正常化，VT/VF抑制	J点正常化，VT/VF抑制	J点正常化，VT/VF抑制	J点正常化，VT/VF抑制	データ少	VT/VF抑制
	isoproterenol	J点正常化，VT/VF抑制	J点正常化，VT/VF抑制	データ少	J点正常化，VT/VF抑制	N/A	N/A
遺伝子変異		*CACNA1C*, *CACNB2B*	*KCNJ8*, *CACNA1C*, *CACNB2B*	*CACNA1C*	*SCN5A*, *CACNA1C*, *CACNB2B*, *GPD1-L*, *SCN1B*, *KCNE3*, *SCN3B*, *KCNJ8*	*SCN5A*	N/A

ERS (early repolarization syndrome)　　（文献[4]より引用改変）

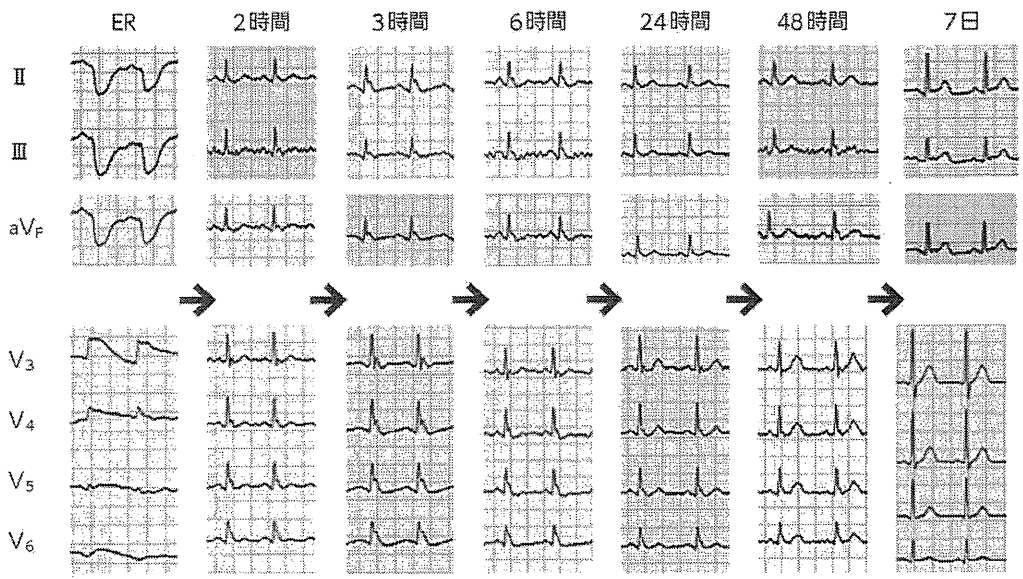

図1　VFを合併したJ-wave症候群の時間的心電図変化
ER (emergency room) で心室細動が認められ，その後広範な誘導に認められていたJ波が時間経過とともに消退していくことが観察できる．

る．また最近では早期再分極のパターンがhorizontal/descendingパターンのものが予後不良とする論文も発表されており[3]，J波の大きさだけでなくST部分の形も重要である．

このように，前胸部誘導にJ波を特徴とするBrugada症候群との間に臨床上様々な類似点が認められることから，Antzelevitchら[4]はこれらをまとめて「J-wave症候群」と命名し，早期再分極症候群をサブタイプに分類することを提唱した（表1）．

J波の成因

J波を認める疾患としては，低体温時に生じるOsborn waveが有名である．このOsborn waveは，Brugada症候群の時と同様に，低温によって生じた心外膜側の活動電位の変化によって説明されている[4]．

Gussakら[5]は，I_{KATP}開口薬およびCa拮抗薬を同時に投与すると，心外膜活動電位のドームが消失（loss of dome）し，心電図上Brugada症候群のST上昇が記録できるが，アセチルコリンのみの投与では，心外膜活動電位のプラトー相が抑制されるのみであるため，ST上昇は軽度でJ波のみを形成したと報告している．その結果としてBrugada症候群に比べ，貫通性の電位勾配が少ないので，早期再分極症候群ではBrugada症候群に比べ不整脈発生も少ないのではないかと推測している．

また，Boineau[6]は，一部のPurkinje線維網が，心筋の筋層深くに侵入していることが原因で一部の心筋が早期に脱分極が終了するため，相対的な脱分極遅延が原因ではないかと推察している．

このようにJ波（早期再分極）の成因については脱分極相，再分極相のいずれの異常でも説明が可能であることが報告されている．

治　療

VF発作が記録されたBrugada症候群ではICDの絶対適応であるのと同様，VFが捉えられたJ-wave症候群でもICDは必須である．J-wave症候群におけるelectrical stormにはBrugada症候群同様，イソプロテレノールの静注が有効であり，再発予防にキニジンが有効であったことが報告されているため，発作時の治療は現時点ではBrugada症候群のそれに準じるべきである．

おわりに

J波，早期再分極パターンは，VF発作直後の心電図のみに認められることもしばしば経験される（図1）．よって今まで突然死例やVF例でも見逃されていたものが多数あったかもしれないことを念頭に，特に発作時の心電図記録を詳細に検討することが大変重要であると考えられる．さらに，原因不明の失神例でも，この症候群を念頭に検査を進めていくことが重要であるが，高い再現性をもってJ波を誘発できる方法の開発が待たれる．

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◈回　答

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草野研吾

不整脈

[要　旨]　不整脈は放置して良いものから，その不整脈が生じるだけで死に至る致死的不整脈まで臨床像は多彩で，不整脈の種類も多い。不整脈の鑑別診断は心電図で行われる。不整脈の種類により治療法が異なるので，心電図診断に習熟することが必要である。心電図では上室不整脈と心室不整脈を鑑別することと，徐脈性不整脈と心室へ伝導しない上室期外収縮の鑑別が基本である。複数の臨床検査を組み合わせることにより不整脈による心臓突然死を予知する試みがなされている。不整脈の生じる背景を把握するための検査として胸部レントゲン，心エコー，運動負荷心筋シンチグラフィー，冠動脈造影，心臓MRIをあげることができる。一方，不整脈の診断とその基質を把握する検査として長時間ホルター心電図，イベントレコーダー，加算平均心電図による心室遅延電位，マイクロボルトレベルのT波交互脈，心臓電気生理学的検査がある。
[キーワード]　不整脈，失神，心電図，心臓電気生理学的検査

不整脈を疑うべき臨床症状

不整脈は正常洞調律以外のすべての心拍を含むので，不整脈があっても症状がない場合からその不整脈になるだけで死に至る場合まで、臨床像は多彩である。症状の程度により不整脈の重症度が決定される（表1）。不整脈が生じているときに症状がない場合は最も重症度が低く，治療の必要もない。脈が飛ぶあるいは脈が抜ける場合には期外収縮による症状であることが多いが，なかには洞停止あるいは洞房ブロックまたは房室ブロックによって脈が抜ける場合がある。胸部違和感，胸痛等の症状を訴える症例のなかには不整脈を生じている場合もあるので注意を要する。動悸がある場合にはおおよそ頻脈性不整脈のことが多いが，一部に徐脈性不整脈が関与していることもある。脈拍が乱れる期外収縮や心房細動でも動悸を自覚するが、脈拍が規則正しくても頻脈であれば動悸を自覚する。特に，突然始まり，しばらく持続した後に突然停止する頻脈性動悸は，発作性頻拍であり，リエントリーによって生じる。眩暈の特徴は「引きずり込まれるような」とか，「目の前が暗くなる」あるいは「白くなる」という表現をすることである。視野が廻るという回転性であったり，ふわふわしたり歩行中にどちらかに片寄っていってしまうような場合は内耳障害や中枢性障害であったり，高血圧による症状であることが多い。眩暈や失神のまえに「胸が締め付けられるような」とか，「少しどきどきしたら」などの形容が付いたら，間違いなく発作性の不整脈によって眩暈が生じたと考えて良い[1]。逆に徐脈性不整脈による失神の場合には突然に意識を消失することが多い。不幸にして突然死する症例のなかに致死的不整脈によって死亡する場合がある。Brugada様心電図を示す症例，QT延長症候群などは自覚症状がなくても突然死に結びつく心室細動を発作的に生じる可能性があるので，心電図所見（図1）が明らかになった時点で必要な検査をして治療を開始するか，経過観察をすべきである。

確定診断に要する検査

基本的に不整脈の診断は心電図により行われる。心電図による不整脈診断の過程は表2に示した。なかでも非通常型心房粗動を含めた上室頻拍の鑑別には電気生理学的検査を要する。幅広QRS波の頻拍に関しても電気生理学的検査を要する[2]。

入院治療か外来治療かの判断

基本的に頻脈性不整脈があって，抗不整脈薬治療を開始するときには入院して抗不整脈薬投与を開始する。外来で投与を開始するときもあるが，抗不整脈薬の副作用は1～2週間以内に出現することが多く，ときに致死的

表1　症状からみた不整脈の重症度

極く軽症	不整脈はあるが，症状はない
軽　症	胸の違和感，気分が悪い，脈がとぶ，胸がつかえる，胸がモヤモヤする
中　症	動悸がする，めまいがする
重　症	意識が無くなる→失神，突然死

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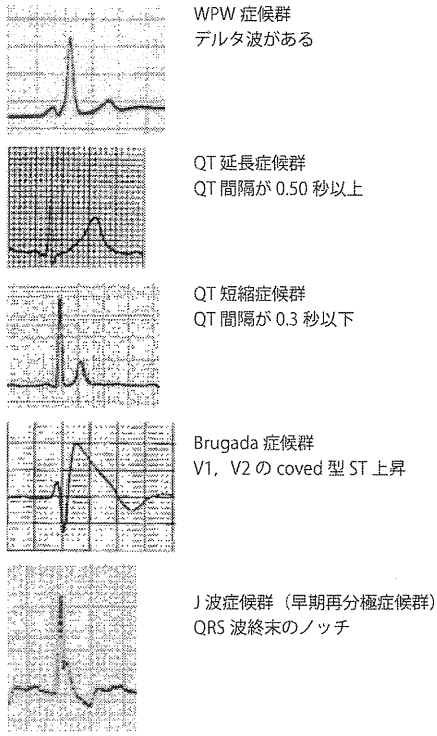

図 1　器質的心疾患がなくても心室細動を生じる可能性のある心電図波形の特徴

となることがあるので，抗不整脈薬投与初期には入院させることが望ましい。外来で抗不整脈薬を投与するときには，少量から開始することと，数日後あるいは 2 週間以内に心電図と自覚症状を必ず確かめることが必要である。カテーテル・アブレーション，ペースメーカー植込み，植込み型除細動器装着などの観血的治療に際しては入院を要する。

不整脈に特徴的な検査

不整脈の診断には心電図所見が必須になるので，診断を正確にするために，自覚症状のある時の心電図を記録できるような工夫が必要で，場合によっては心臓電気生理学的検査による電気刺激で不整脈を誘発して，自覚症状と合致するか確かめる必要がある。

不整脈の性質あるいは不整脈を生じる基質の有無を把握する検査として，ホルター心電図検査，イベントレコーダー，加算平均心電図による心室あるいは心房遅延電位検出，マイクロボルトレベルの T 波交互脈検出（T Wave Alternans：TWA）[3]、心臓電気生理学的検査があげられる。また，トレッドミル運動負荷心電図による不整

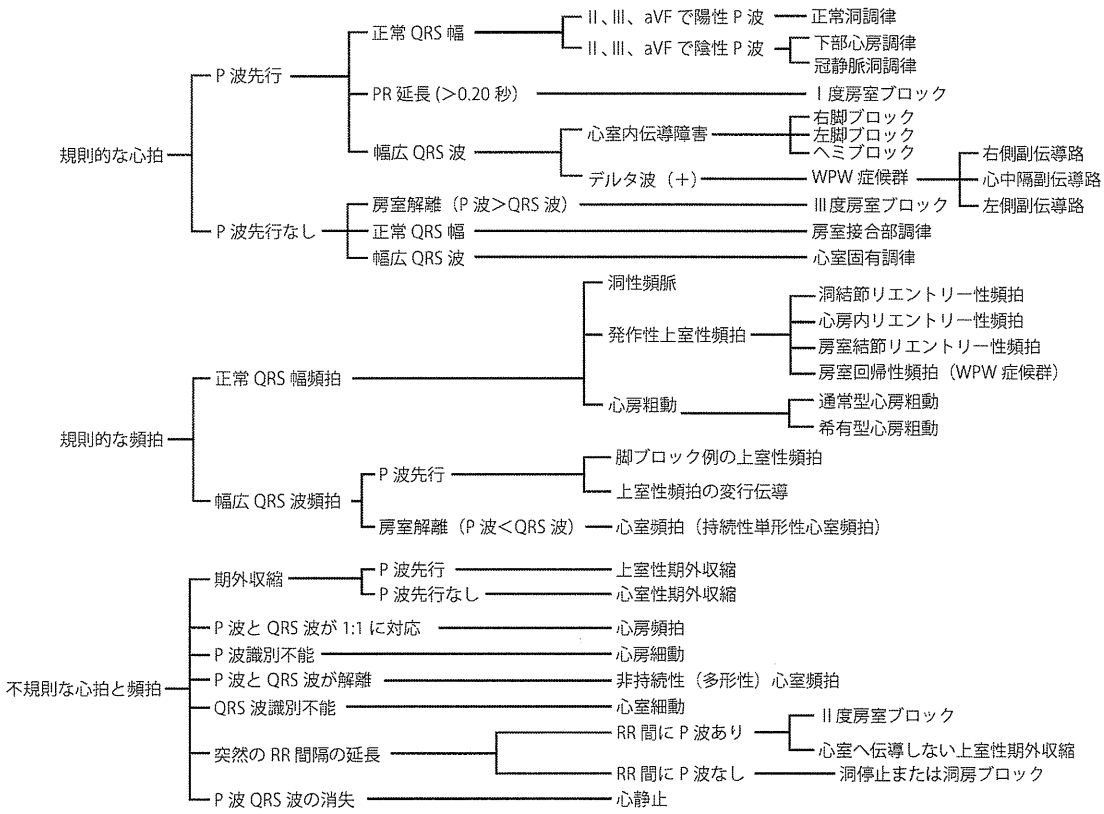

図 2　心電図による不整脈診断（第 1 章　検査値アプローチ編・心電図検査 72 ページ参照）

表3　不整脈に関連する検査

不整脈自体の診断	不整脈の性質診断	不整脈を生じる背景の診断
① 12 誘導心電図	① ホルター心電図	① 血液検査（甲状腺，カテコラミンなど）
② 運動負荷心電図	② 心室遅延電位検出	② 胸部レントゲン
③ ホルター心電図	③ TWA 検出	③ 心エコー
④ イベントレコーダー	④ QTd	④ 心筋シンチグラフィー
⑤ モニター心電図	⑤ 心臓電気生理学的検査	⑤ 冠動脈造影
⑥ 心臓電気生理学的検査		⑥ 心臓 MRI

脈の誘発，強制立位試験（head-up tilt 試験：ヘッドアップチルト試験）による失神の鑑別，12 誘導心電図を用いた QT 間隔のゆらぎ（QT dispersion）なども不整脈に関連した検査である。不整脈の生じる背景を把握するための検査として胸部レントゲン，心エコー，運動負荷心筋シンチグラフィー，冠動脈造影，心臓 MRI[4] による delayed enhancement をあげることができる（表 3）。

治療後の経過観察に必要な標準的検査

過去にはカテーテル・アブレーションの有効性を確かめるために，アブレーション 1 週間後に再度電気生理学的検査を行うこともあったが，高周波カテーテル・アブレーションが確立された治療法となってからは，外来で経過観察するようになっている。したがって，アブレーション後の検査としては 12 誘導心電図，胸部レントゲン，ホルター心電図検査，心エコー検査などであるが，いずれも退院後の外来検査として行うことができる。

ペースメーカー植込み直後と 1 週間後には胸部レントゲンで心内リードの位置を確認する。同時に 12 誘導心電図を記録する。植込み 1 週間後にペースメーカーチェックをして退院となる。植込み型除細動器に関しても同様であるが，1 週間後に病室で心室細動を誘発して除細動器が作動するか確認している。退院 1 ヶ月後にペースメーカー外来あるいは ICD 外来を受診して 12 誘導心電図と胸部レントゲンをとり，ジェネレーターの点検を行っている。

治療による副作用チェックのための検査

抗不整脈薬治療を行っているときにはこまめに心電図を記録することが大切である。採血による血中濃度測定も必要であるが，催不整脈作用を察知するには心電図による QT 間隔の変化と，QRS 幅の変化に注意を要する。ナトリウムチャネル遮断薬（Ⅰ群薬）を服用中には QRS 幅の変化，カリウムチャネル遮断薬を服用中には QT 間隔の変化に注意する（表 4）。

専門医にコンサルテーションするポイント

不整脈は機能的な疾患であり，不整脈が生じていないときに診察しても正常である例は多い。もし，発作性頻拍のある患者であっても，頻拍時の心電図がなければ診断は困難である。不整脈記録がない場合に参考になるのが自覚症状である。不整脈による自覚症状が疑われたら専門医へコンサルタントしておく方がよい。動悸がある場合にはおおよそ頻脈性不整脈のことが多いが，一部に徐脈性不整脈が関与していることもある。脈拍が乱れる期外収縮や心房細動でも動悸を自覚するが、脈拍が規則正しくても頻脈であれば動悸を自覚する。特に，突然始まり，しばらく持続した後に突然停止する頻脈は，発作性頻拍であり，リエントリーによって生じる。このような頻拍はホルター心電図や 12 誘導心電図で記録できなくても，電気生理学的検査で誘発可能であり，専門医へ紹介すべきである。

自覚症状として重症度の高いのは，眩暈や失神・意識消失発作である（表 1）。徐脈性不整脈でも頻脈性不整脈でも生じうる。このような自覚症状を訴える場合にはすぐに専門医へ紹介すべきである。

不整脈患者の紹介に際して，可能ならば不整脈時の心電図があると診察は円滑にすすむ。不整脈の診断は心電図で行なわれるので，今後の必要な検査が選択できるし，治療法の選択も早い。もし，心電図記録があるなら是非紹介状に添えていただけると有益である。記録の汚い心電図でもモニター心電図でも役に立つことは多い。WPW 症候群でも間欠性の場合には，病院受診時に正常 QRS 波を呈していることもあり，デルタ波の記録されている心電図があれば，診断過程の無駄な時間がなくなる。

徐脈性不整脈であれば，隣接する RR 間に心室へ伝導しない P 波が 2 つ以上ある高度房室ブロック[5] と，洞停止あるいは洞房ブロックを示す洞不全症候群の所見があれば専門医へ紹介すべきである。頻脈性不整脈のうち，自覚症状の強い期外収縮，頻発する期外収縮，心房細動，非持続性心室頻拍については，専門医を受診するように勧める。不整脈は単に表に現れている現象であって，背

表4　抗不整脈薬の催不整脈要因

抗不整脈薬	左室への影響	排泄経路(%)	催不整脈要因	心臓外の副作用
リドカイン	→	肝	(QRS 幅拡大)	ショック，嘔吐，痙攣，興奮
メキシレチン	→	肝	(QRS 幅拡大)	消化器症状，幻覚，紅皮症
プロカインアミド	↓	腎(60)，肝(40)	QT 延長，QRS 幅拡大	SLE 様症状，顆粒球減少，肝障害
シソピラミド	↓	腎(70)	QT 延長，QRS 幅拡大	口渇，尿閉，排尿困難，低血糖
キニジン	→	肝(80)，腎(20)	QT 延長，QRS 幅拡大	Cinchonism(眩暈など)，消化器症状
プロパフェノン	↓	肝	QRS 幅拡大	筋肉痛，熱感，頭痛，悪心，肝障害
アプリンジン	→	肝	QRS 幅拡大(QT 延長)	しびれ，振顫，肝障害，白血球減少
シベンゾリン	↓	腎(80)	QRS 幅拡大	頭痛，眩暈，口渇，尿閉，低血糖
ピルメノール	↓	腎(70)	QT 延長，QRS 幅拡大	頭痛，口渇，尿閉
フレカイニド	↓	腎(85)	QRS 幅拡大	眩暈，耳鳴，羞明，霧視，下痢
ピルジカイニド	↓→	腎	QRS 幅拡大	消化器症状，神経症状(ともに少ない)
ベプリジル	→	腎(50)	QT 延長，徐脈	眩暈，頭痛，便秘，肝障害，倦怠感
ベラパミル	↓	肝(80)，腎(20)	徐脈	便秘，頭痛，顔面のほてり
ジルチアゼム	↓	肝(60)，腎(35)	徐脈	消化器症状，ほてり
ソタロール	↓	腎(75)	QT 延長，徐脈	気管支喘息，頭痛，倦怠感
アミオダロン	→	肝	QT 延長，徐脈	肺線維症，甲状腺機能異常，角膜色素沈着
ニフェカラント	→	腎(50)，肝(50)	QT 延長	口渇，ほてり，頭重感
β-遮断薬	↓	肝，腎	徐脈	気管支喘息，血糖値低下，脱力感，レイノー現象
アトロピン	→	腎	頻脈	口渇，排尿障害，緑内障悪化
ATP	→	腎	徐脈	頭痛，顔面紅潮，悪心，嘔吐
ジゴキシン	↑	腎	ジギタリス中毒	食欲不振，嘔吐

後に器質的心疾患が隠れている場合も多いからである。

発作性心房細動・粗動，発作性上室頻拍，持続性心室頻拍のような発作時の心電図が記録されていれば，治療目的で紹介すべきである。現在発作が生じている場合には近くの専門医へ速やかに転送する。非発作時であっても専門医へ紹介すれば，非観血的治療も含め，患者にとっては最良の治療法を選択することができる。クリニックや診療所にとって，大病院へ紹介する利点は，設備投資のかかる医療を代行してくれることと，治療時間のかかる医療を代行してくれることである。不整脈治療に関してこれに相当するのはカテーテル・アブレーション，植込み型除細動器であり，アミオダロンやベプリジルなどの特殊な抗不整脈薬治療やペースメーカー治療も含まれる。

保険診療上の注意

抗不整脈薬のなかには頻脈性不整脈治療の適応はとれていてもおおよそは心室不整脈が対象になっている。心房細動を含めた上室不整脈の適応がとれていない抗不整脈薬もあるのでこのことは念頭に置いておく。

心室遅延電位と TWA は Brugada 症候群や陳旧性心筋梗塞のハイリスク群を予知するために有用であり，平成23年度から保険適応になった。

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Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

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]

Editorial p586

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.

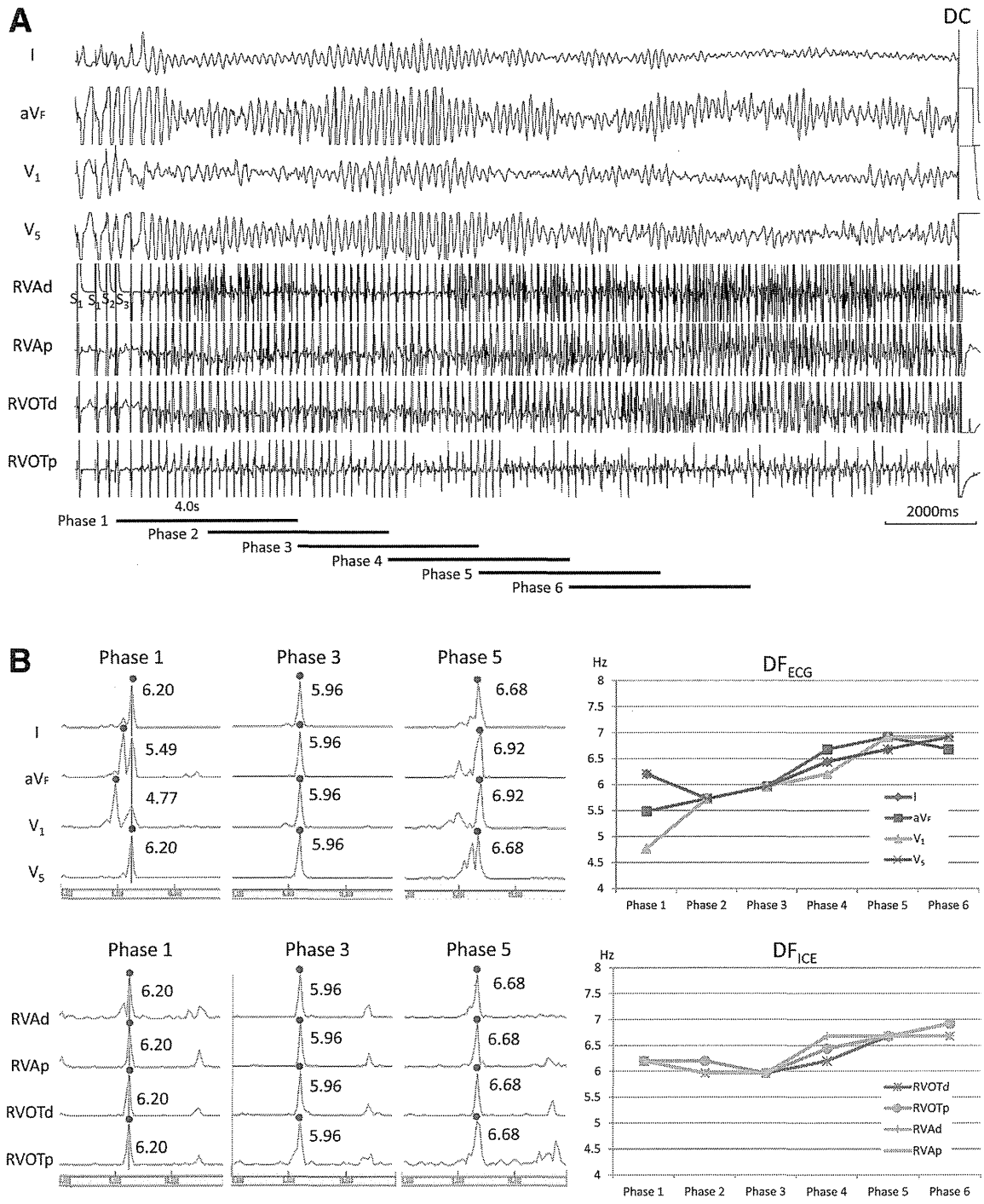

Figure 1. Representative case of induced ventricular fibrillation (VF) in a symptomatic Brugada syndrome patient. (**A**) Surface electrocardiograms (ECGs) and intracardiac electrograms from a 63-year-old man referred for further examination because of a history of syncope and Brugada-type ECG. VF was 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.

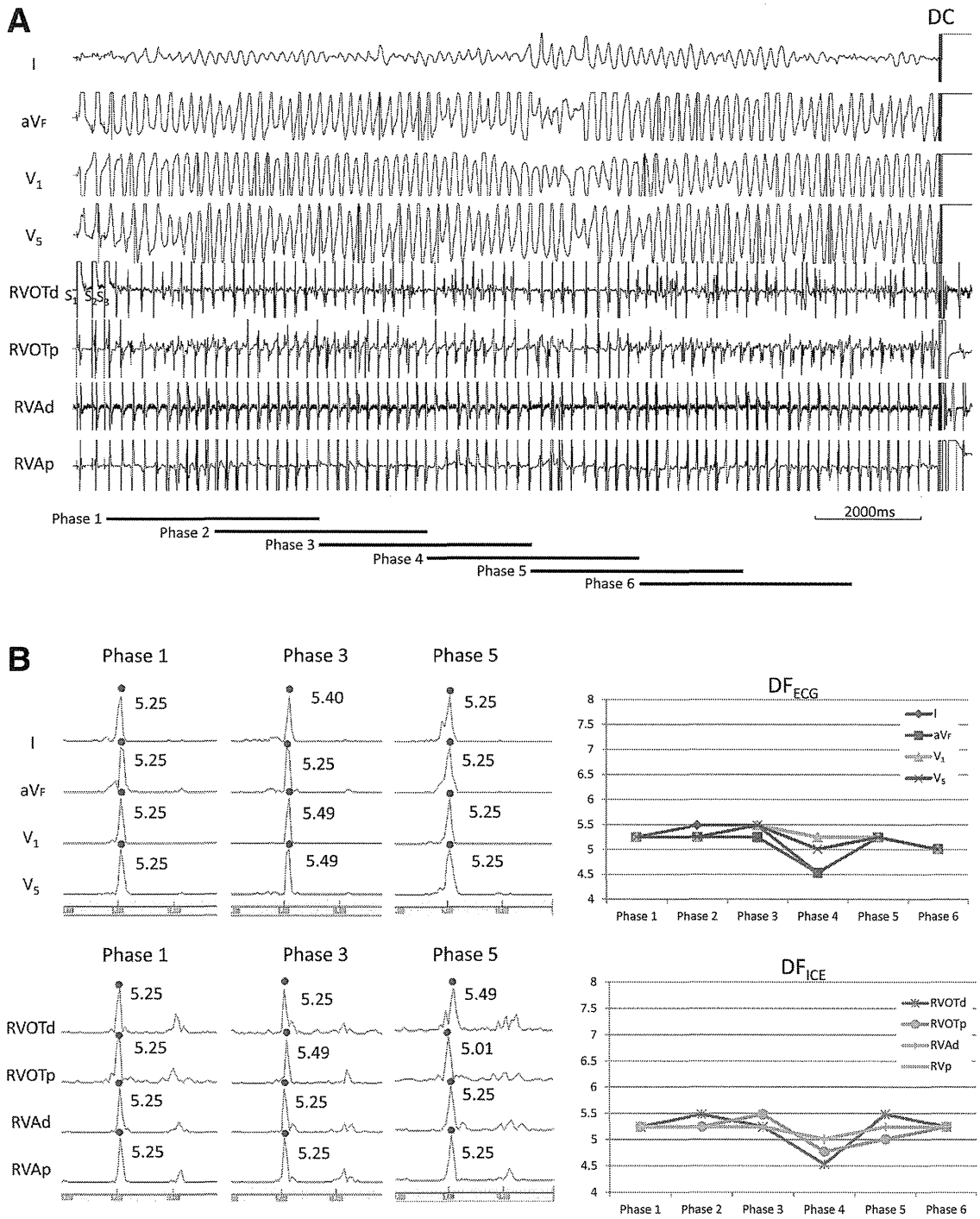

Figure 2. Representative case of induced ventricular fibrillation (VF) in an asymptomatic Brugada syndrome patient. (**A**) Surface electrocardiograms (ECGs) and intracardiac electrograms (ICE) from a 26-year-old man with asymptomatic Brugada syndrome referred for further examination of a Brugada-like 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-

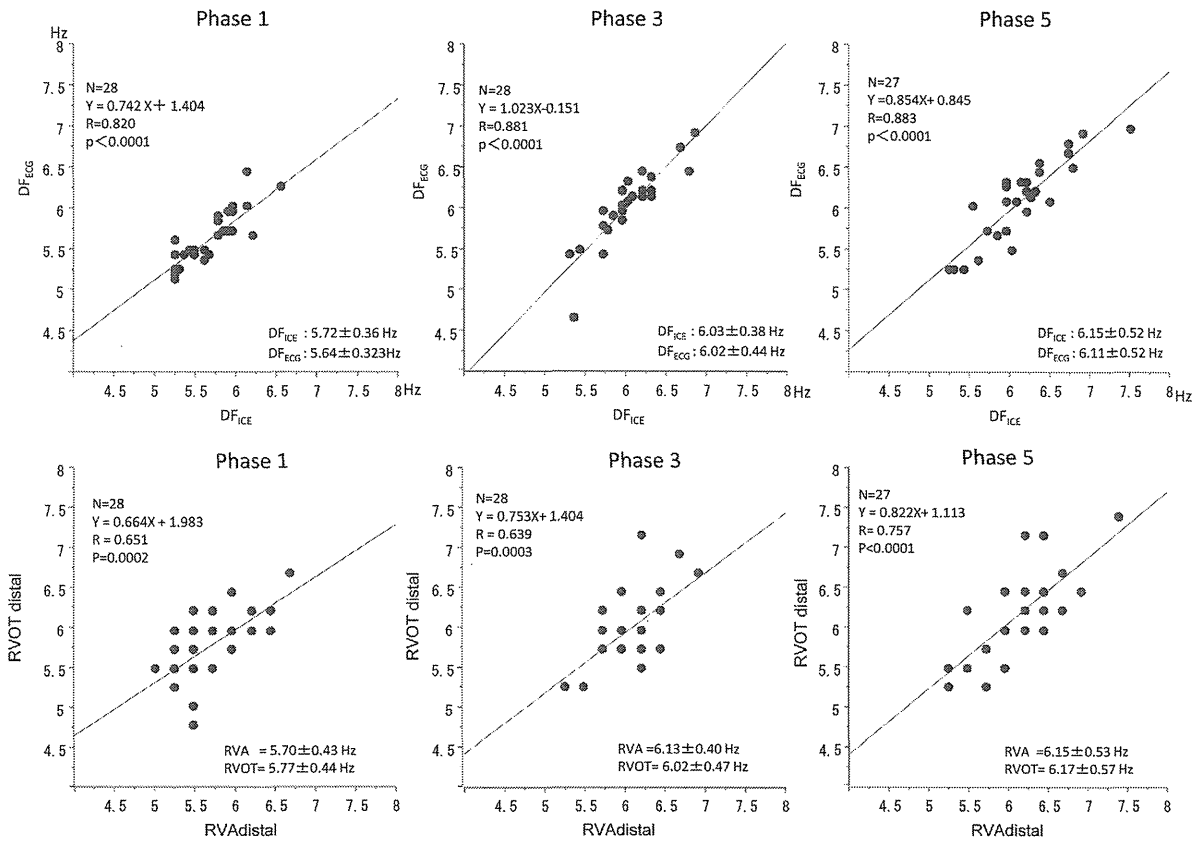

Figure 3. Relationship between dominant frequency (DF) from surface electrocardiograms (DF_{ECG}) and intracardiac electrograms (DF_{ICE}) and relationship of DF between the right ventricular apex (RVA) and RV outflow tract (RVOT) distal pairs. DF_{ECG} and DF_{ICE} show a significant relationship in 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.

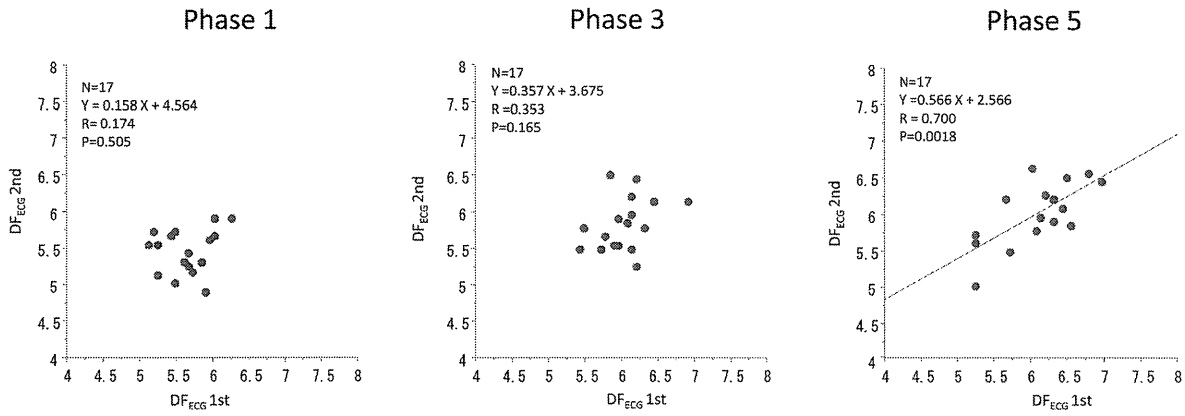

Figure 4. Dominant frequency (DF_{ECG}) reproducibility. A significant relationship is observed for DF_{ECG} between the first (X axis) and second ventricular fibrillation (Y axis) episodes in phase 5.

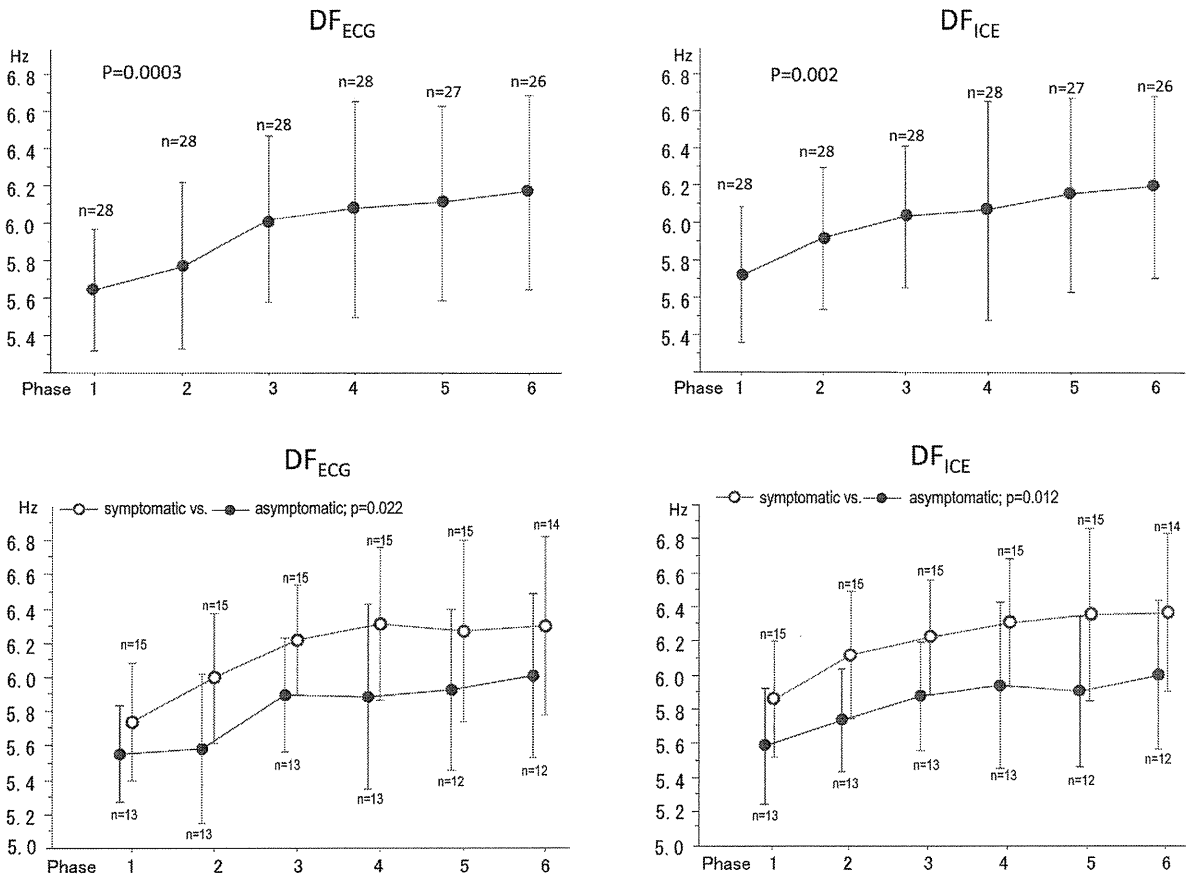

Figure 5. Transition of dominant frequency (DF_{ECG} and DF_{ICG}) with phase. (**Left**) DF_{ECG} change for all patients (**Upper**) and symptomatic and asymptomatic groups (**Lower**). (**Right**) DF_{ICE} change for all patients (**Upper**) and symptomatic and asymptomatic groups (**Lower**).

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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Journal of Cardiology 60 (2012) 47–54

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Original article

Effects of isoproterenol and propranolol on the inducibility and frequency of ventricular fibrillation in patients with Brugada syndrome

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ARTICLE INFO

Article history:
Received 8 October 2011
Received in revised form 17 January 2012
Accepted 13 February 2012
Available online 21 March 2012

Keywords:
Brugada syndrome
Ventricular fibrillation
Fast Fourier transform
Isoproterenol
Propranolol

ABSTRACT

Background: Isoproterenol (ISP), a beta-adrenergic agonist, suppresses arrhythmic storm in patients with sporadic Brugada syndrome (BS). However, the influence of ISP and the beta-adrenergic antagonist propranolol (PRO) on the inducibility and frequency of ventricular fibrillation (VF) in BS patients remains unclear.

Methods and results: Twenty-seven BS patients with induced VF > 10 s in a control state were enrolled. Electrophysiological stimulation (EPS) testing was performed during ISP and after PRO in selected patients. The inducibility and frequency of VF were compared. Dominant frequency (DF) was obtained by Fast Fourier transform from 4-s data (phase) and sequentially every 2 s up to phase 5. ISP prevented induction of VF in 20 of 25 patients (80%). During ISP, 5 patients experienced induction of VF. ISP significantly influenced DF transition compared with the control state. DF gradually increased but was unchanged after the middle phase. PRO had no effect on incidence of induced VF in 5 patients; increased PRO induced VF in 5 (83.3%) of 6 patients who tested negative during ISP. After PRO, 10 patients experienced induction of VF. Thus, PRO significantly influenced DF transition. DF after PRO was higher than that in the corresponding phase in the control state.

Conclusion: ISP suppressed induction of VF and the increase of DF with time. PRO aggravated VF and accelerated DF.

Introduction

Brugada syndrome (BS) is an arrhythmogenic disease characterized by an electocardiographic (ECG) pattern of the right bundle branch block, ST-segment elevation in the right precordial leads, and an increased risk of sudden cardiac death as a result of polymorphic ventricular tachyarrhymias or ventricular fibrillation (VF) in patients without apparent organic heart disease [1,2]. Autonomic function has been suggested to be related to VF in BS [3]. VF has been induced with vagal activity in patients with BS [4]. ST-segment elevation is mitigated by administration of beta-adrenergic agonists and is enhanced by parasympathetic agonists such as acetylcholine in experimental and clinical investigations [3–7]. The beta-adrenergic stimulator isoproterenol (ISP) has been reported to suppress arrhythmic storm in patients with sporadic BS [7]. However, the beta-adrenergic antagonist propranolol (PRO) has no potential to suppress VF in patients with BS [4].

Fast Fourier transform (FFT) was used as a method of analyzing VF cycle length [8–11] and atrial fibrillation [12,13]. Spectral analysis via FFT is also useful to characterize induced and spontaneous VF cycle length [14,15]. However, information is scarce about FFT analysis of ventricular electrograms during VF, especially in patients with BS [15].

The purpose of this study was to investigate the effects of ISP and PRO on the inducibility and frequency of VF using FFT analysis in patients with BS.

Methods

Subjects

This study was conducted between November 2003 and April 2011. Forty-three patients were enrolled. Of these, 27 males (age 50.5 ± 14.0 years; 14 symptomatic and 13 asymptomatic) who

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doi:10.1016/j.jjcc.2012.02.001