1）QT 延長と医薬品との関係について継続調査を進めると共に、2）先天性・後天性（二次性）QT 延長が女性に多い点を、実験動物の心室筋標本で評価したいと考え、QT 延長や TdP 発生と関係するアドレナリン受容体（表１）の雌雄の量的・質的違いについて放射性標識化合物（ラジオアイソトープリガンド）を用いた結合実験で検討を加えることを目的とした。

＜QT 延長と関係する医薬品＞

独立行政法人・医薬品医療機器総合機構が管理している web サイト「医薬品医療機器情報提供ホームページ」(http://www.info.pmda.go.jp/) 内の「医療用医薬品の添付文書情報」を利用し、「QT 延長」で検索をしたところ、2004 年 9 月 14 日現在、552 件がヒットした。そのうち 295 件が「重大な副作用」、「その他の副作用」あるいは「重要な基本的注意」の項目に記載されており、これらが単剤で QT 延長を引き起こす可能性のあることがわかった。また残りの 257 件は、他の薬剤との併用で QT 延長の可能性がある薬剤であった(主に Ca 拮抗薬と利尿薬)。表 2 には、単剤で QT 延長を引き起こす可能性のある薬剤を、商品名で分類した全 219 件を示す。表 3 には、一般名で分類した全 68 件を示す。また図１には、上記の QT 延長を引き起こす可能性のある薬剤の用途別割合を示した。

以上の検索結果より、QT 延長を引き起こす可能性のある薬剤の種類は研究開始初年度より更に増加し、循環器作用薬よりも非循環器作用薬のほうが圧倒的に多く、統合失調症治療薬＞抗不整脈薬＞抗菌薬＞抗悪性腫瘍薬・抗鬱薬＞抗真菌薬・消化器作用薬＞高脂血症治療薬・骨粗鬆症治療薬＞その他の順であることがわかった。

＜心室筋におけるアドレナリン受容体結合性の雌雄差＞

ＴｄＰ発現と密接に関係するα_1-およびβ-アドレナリン受容体に焦点をしぼり、動物実験においてこれら心筋受容体の量的・質的な雌雄差について検討を加えた。

その結果、α_1-アドレナリン受容体への[^{3}H]prazosin の結合性は、受容体親和性の指標となるＫｄ値が雄性で０．２７±０．０３ｎＭ、雌性で０．１６±０．０２ｎＭであり、受容体結合量の指標となる Bmax 値が雄性で８４．２±７．８fmol/mg protein、雌性で７８．６±８．２fmol/mg protein であった。一方、β-アドレナリン受容体への[^{3}H]CGP12177 の結合性は、受容体親和性の指標となるＫｄ値が雄性で０．８９±０．０９ｎＭ、雌性で０．６５±０．０７ｎＭであり、受容体結合量の指標となる Bmax 値が雄性で２６．３±４．３fmol/mg protein、雌性で３２．５±５．２fmol/mg protein であった。

以上のラジオレセプターアッセイの成績から、ラット心筋アドレナリン受容体において量的違いは雌雄間で検出されなかったが、これら受容体の質的変化（親和性の増大）が存在しており、女性で多発するＱＴ延長症候群との関連性が示唆された。

先天性・後天性（二次性）の QT 延長症候群の解明が進むにつれ、あらかじめ QT 延長の可能性がある薬剤は避けるなど、個々の患者さんに合った治

療方針が立てられることが必要である。

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表１　TdP を誘発させる生理作用とその発現機序

生理作用	発現機序
Na電流（I Na）増強作用	Na電流増強→内向き電流増加→ APD* 延長→再分極遅延→ EAD 発生→QT延長→TdP
K電流（IK）抑制作用	活動電位第3相IK* 抑制→APD* 延長→再分極遅延→ EAD 発生→QT延長→TdP
Ca電流（I Ca）増強作用	内向き電流増加→APD* 延長→再分極遅延→ EAD 発生→QT延長→TdP
?$_1$受容体活性化	Ito*減少によりAPD* 延長→再分極遅延→ EAD 発生→QT延長→TdP
?受容体活性化	Gs蛋白質活性化→ cAMP 増加→PK-A 活性化→L型Caチャネルリン酸化→ICa 増大
血清K値低下作用	心室筋のKに対する透過性減少→IK* 減少
血清Mg値低下作用	MgによるCa心筋細胞流入阻害作用の低下→内向き Ca電流増加
徐脈作用	逆頻度依存性→IKr* 抑制効果増大
Naチャネル抑制作用	第0相の内向きNa電流抑制→ APD* 延長→再分極遅延→ EAD 発生→QT延長→TdP

*APD：活動電位持続時間　*Ito：一過性外向きK電流　*IK：外向き遅延整流K電流　*IKr：活性化の速いIK

表２　単剤で QT 延長を引き起こす可能性のある薬剤（商品名分類）

統合失調症治療薬			抗不整脈薬	
アナテナジン	セレネース	フルメジン	アジマリン	ピメノール
アナテンゾール	ソフミン	ブロムペリドール	アスペノン	ファンミル
アビリット	トーピリド	ブリペリドール	アプリトーン	プロノン
イリヤキン	トリオミン	ブリンドリル	アプリペノン	**ベプリコール**
インプロメン	トリフロペラジン	ブロクラジン	アミサリン	ボエルテン
ウインタミン	トリラホン	ブロピタン	アンカロン	ボストルミン
エセックチン	トロペロン	ベゲタミン	オルゾロン	ミコルテン
オーラップ	ドグマチール	ベタマックT	カフィール	メキシチール
クールスパン	ニチマール	マーゲノール	サンリス	メキシバール
クレミン	ニューレプチル	ミラドール	サンリズム	メキシレート
コスミナール	ネオペリドール	メルカイック	シペノール	メキトライド
コントミン	ノバミン	メレリル	シンビット	メキラチン
シーグル	ハロジャスト	ヨウペリドール	ジソピラ	メトレキシン
スイロリン	ハロステン	ヨウマチール	ジソピラン	メルデスト
スカノーゼン	ハロペリドール	リスパダール	ソタコール	メレート
スタドルフ	ハロマンス	リントン	ソピラール	モバレーン
スタマクリット	ハロミドール	ルナプロン	ソピラート	リスピン
スピロピタン	バチール	ルバトレン	タイリンダー	リスモダン
スプロチン	バルネチール	レボトミン	タンボコール	リスラミド
スペサニール	ピーゼットシー	レボホルテ	チヨバン	リズムコート
スルピリド	ヒルナミン	レモナミン	チルミメール	リゾラミド
セルマニル	フルデカシン	塩酸クロルプロマジン	トイ	ロバフール
		（66件）	ノルペース	硫酸キニジン （46件

消化器作用薬	抗真菌薬	抗菌薬	高脂血症治療薬	抗うつ薬	その他
アセナリン	アルナゾール	エシノール	イエスタミン	アナフラニール	アーキンZ
オメプラゾール	コランゾール	エリスロシン	エタクレート	アンデプレ	（強心薬）
ガスイサン	ジフルカン	エリスロマイシン	エバチコールP	イミドール	アリセプト
ガスセプト	ニコアゾリン	**クラリシッド**	クラフェデン	クロンモリン	（アルツハイマー病薬）
ガスター	ビスカルツ	クラリス	コバクス	デジレル	エバステル
ガスドック	フェミナゾール	ザイボックス	サクベルコート	トフラニール	（Hブロッカー）
ガスペラジン	フラノス	ジスロマック	シンレスタール	ノイオミール	タラモナール
ガスポート	フルカード	スオード	スイムタール	ノリトレン	（麻酔剤）
ガスメット	フルカジール	スパラ	ダウンオイール	マプロミール	ドロレプタン
ガスリック	フルコナール	タカスノン	ピヨコール	ルジオミール	（麻酔用神経遮断剤）
ガモファー	フルコナゾール	ルリッド	フッコラート	レスリン	バップフォー
クリマーゲンE	フルコナゾン		プロスエード		（尿失禁・頻尿治療剤）
ケミガスチン	フルコナメルク		プロプコール		ランサップ
ケラモ	フルゾール	（11件）	プロプコリン	（11件）	（H.pylori除菌薬）
ストマルコン	フルゾナール	抗悪性腫瘍薬	プロプレタン	骨粗鬆症治療薬	レビトラ
チオスター	フルタンゾール	アルケラン	ライドラース	オンクラスト	（勃起不全薬）
ハーフタツミ	フルラビン	イレッサ	リボプコール	テイロック	ロカルトロール
ファスタニール	フロリードF	オペプリム	ロルスター	フォサマック	（副甲状腺機能亢進症薬）
ファモガスト	プロジフ	カルセド	ロレルコ	ボナロン	輸血用チトラミン
ファモスタジン	ベナンバックス	フルツロン	ワニール		（血液凝固防止薬）
ファモチジン	ミコシスト				ホスカビル
プロスターM					（サイトメガロウイルス薬
プロゴーギュ					
モミアロン					
（24件）	（21件）	（5件）	（20件）	（4件）	（11件

表3　単剤でQT延長を引き起こす可能性のある薬剤（一般名分類）

統合失調症治療薬	抗不整脈薬	抗菌薬	抗悪性腫瘍薬	その他
クロルプロマジン	アジマリン	アジスロマイシン	アムルビシン	エバスチン
スピペロン	アプリンジン	エリスロマイシン	ゲフィチニブ	カルシトリオール
スルトプリド	アミオダロン	**クラリスロマイシン**	ドキシフルリジン	クエン酸Ｎａ
スルピリド	キニジン	スパルフロキサシン	ミトタン	ドネペジル
チオリダジン	ジソピラミド	プルリフロキサシン	メルファラン	ドロペリドール
チミペロン	シベンゾリン	リネゾリド	（5件）	バルデナフィル
トリフロペラジン	ソタロール	ロキシスロマイシン	抗うつ薬	プロピベリン
ハロペリドール	ニフェカラント	（7件）	イミプラミン	ベスナリノン
ピモジド	ピルジカイニド	抗真菌薬	クロミプラミン	ホスカルネットＮ
フルフェナジン	ピルメノール	フルコナゾール	トラゾドン	
プロクロルペラジン	フレカイニド	ペンタミジン	ノルトリプチリン	
プロペリシアジン	プロカインアミド	ミコナゾール	マプロチリン	
ブロムペリドール	プロパフェノン	（3件）	（5件）	
フロロピパミド	**ペプリジル**	消化器作用薬	高脂血症治療薬	
ペルフェナジン	メキシレチン	オメプラゾール	プロブコール	
モサプラミン		シサプリド	（1件）	
モペロン		**ファモチジン**	骨粗鬆症治療薬	
リスペリドン			アレンドロン酸Ｎａ	
レボメプロマジン				
（19件）	（15件）	（3件）	（1件）	（9件

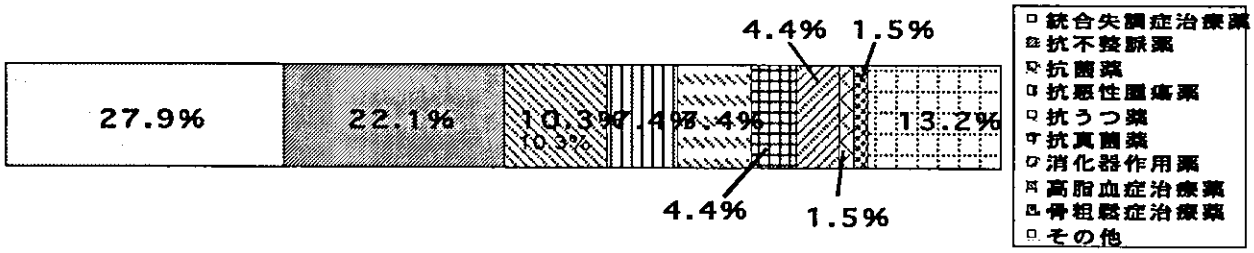

図1　QT延長を引き起こす可能性のある薬剤の用途別割合

厚生労働科学研究費補助金（医薬安全総合　研究事業）
分担研究報告書

先天性 QT 延長症候群の遺伝子型の推定と潜在性 QT 延長症候群の検出
- エピネフリン負荷試験の有用性 -

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研究要旨： LQT1 型の 31 例、LQT2 型の 23 例、LQT3 型の 6 例、対照群 30 例にエピネフリン(Epi)負荷試験を施行した。Epi 点滴中の定常状態の QTc を用いると、LQT1 型と LQT2 型の診断率は向上し(68%→87%、83%→91%)、LQT3 型は不変であった(83%)。QTc 延長(Epi 定常状態)≥35ms は LQT1 型、QTc 延長(定常状態)<35ms かつ QTc 延長(peak)≥80ms は LQT2 型、それ以外は LQT3 型または正常者と推定された。Epi 負荷は、先天性 LQTS の遺伝子型の推定と潜在性 QT 延長症候群の検出に有用

A. 研究目的

先天性 QT 延長症候群(LQTS)は、心電図上の QT 時間の延長と Torsade de Pointes (TdP)と称される多形性心室頻拍を認め、失神や突然死の原因となる疾患であり、現在までにイオンチャネル機能に関係する 8 つの遺伝子型が報告されている。特に遺伝子診断される患者の 90%以上を占める LQT1、2、3 型では、遺伝子診断率の向上に伴い、遺伝子型と表現型の関連、すなわち遺伝子型別の臨床病態の違い、あるいは遺伝子型特異的な治療法の可能性が明らかとなってきた。一方、遺伝子異常をもっていながら安静時の QT 時間が正常範囲で失神などの発作の既往がなく、臨床的には LQTS と診断されない、いわゆる非浸透患者(non-penetrant mutation carrier)が予想以上に多く存在することも最近明らかとなってきた(不完全浸透)。また、遺伝子診断率は 50-60%であり、遺伝子診断が可能な施設も限られることから、臨床的に遺伝子型を推定することは重要である。

B. 研究方法

LQT1 型の 31 例(12 家系)、LQT2 型の 23 例(12 家系)、LQT3 型の 6 例(3 家系)、対照群 30 例を対象とし、交感神経刺激薬であるエピネフリン(Epi)負荷試験(0.1μg/kg ボーラス静注 + 0.1μg/kg/分持続点滴)を施行し、先天性 LQTS の遺伝子型の推定、および潜在性 QT 延長症候群の検出における Epi 負荷試験の有用性を検討した。

（倫理面への配慮）

先天性 LQTS 患者の遺伝子診断は、国立循環器病センター倫理委員会の承認を得て行った。Epi 負荷試験は日常臨床負荷試験として施行した。研究成果の発表においては、患者のプライバシーを考慮し、人権擁護を保持する。

C. 研究結果

LQT1 患者では、Epi 開始直後に QTc

時間が著明に延長(_126 }7 ms)し、持続点滴中の定常状態でも QTc 時間延長が持続(_79 }7 ms)するのに対して、LQT2 患者では、Epi 開始直後には一過性に著明な QTc 延長(_124 }4 ms)を認めるが、定常状態では QTc はコントロールレベル近くまで短縮した(_15 } ms)。これに対して LQT3 患者では、Epi 開始直後の QTc 延長は軽度(_34 }9 ms)で、定常状態での QTc はコントロールレベル以下に短縮した(_-11 }0 ms)。

(1) Epi 点滴中の定常状態の QTc を用いると、Keating の診断基準を用いた場合 LQT1 型の診断率は 68%から 87%へ、LQT2 型の診断率は 83%から 91%へと向上した。特異度はいずれも 100%であり正常者で疑陽性になることはなかった。LQT3 型では診断率は 83%のままであった。

(2) Epi 定常状態で QTc が 35ms 以上延長した場合は LQT1 型、定常状態の QTc 延長は 35ms 未満であるが、peak での QTc 延長が 80ms 以上の場合は LQT2 型、それ以外の場合は LQT3 型または正常者と推定された。

D. 考察

以前から、LQTS 家系の家族構成員の中で、QT 時間が境界または正常範囲であるにもかかわらず失神発作などの心事故を認める患者が少なからず存在することが報告され、不完全浸透の可能性が示唆されていた。今回の結果から、特に LQT1 患者における Epi 負荷、心電図学的診断率の向上に有用であることが示された。LQT1は最も頻度の多い遺伝子型であり、運動中、特に水泳中などの交感神経緊張時にTdPが多いことが報告されている。このため、遺伝子診断されていない家系でも、発端者が運動中に心事故を認めLQT1が疑われる場合には、家族構成員全員にEpi負荷試験を施行する意義があるものと考えられる。Epi負荷試験によりmutation carrierである可能性が示唆されれば、運動制限や場合によってはβ遮断薬を開始することにより、心事故を未然に防げる可能性があると考えられる。

一方、遺伝子診断により遺伝子型が同定されれば、心事故の誘因を避けこれを予防することが可能となるが、遺伝子診断率は現在でも50-60%である。また遺伝子診断が可能な施設が限定されること、さらに経費がかかることなどから、臨床的に遺伝子型を推定することは重要である。最終的には遺伝子診断の結果を待たなくてはならないが、LQTS患者におけるEpi負荷試験は、遺伝子診断前に遺伝子型を推定する上で有用であると考えられた。また、遺伝子診断されない40-50%のLQTS患者では、Epi負荷試験に対する反応から遺伝子型を推定し、これに基づいて治療方針を立てる可能性も示唆される。

E. 結論

Epi 負荷試験は、LQT1、2、3 型の遺伝子型の推定、および特に浸透率の低い LQT1 型の臨床診断率の向上やに有用であった。

F. 健康危険情報　　なし

G. 研究発表

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H. 知的財産権の出願・登録状況
(予定を含む。)

なし

別紙５

研究成果の刊行に関する一覧表レイアウト

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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心電図診断

102

エピネフリン負荷による潜在性QT延長症候群の診断と遺伝子型の推定

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QT延長症候群の臨床診断

QT延長症候群（LQTS）は，心電図上のQT時間延長とtorsades de pointes（TdP）型の多形性心室頻拍を認める症候群である．先天性LQTSの臨床診断は，QT時間，臨床症状，家族歴などを考慮したKeatingまたはSchwartzの診断基準に準じて行われる．

Keatingの診断基準　無症候性の場合は修正QT（QTc）≧470msec，または，男性はQTc≧440msec，女性はQTc≧460 msecで，かつ①ストレスに伴う失神，②TdP，③35歳以下の突然死の家族歴，のうち1つ以上を認めれば診断される．

Schwartzの診断基準　臨床所見を点数化し，合計が4点以上で診断確実，2または3点は疑い，1点以下は可能性が低いと判定する．

先天性LQTSでは7つの遺伝子型が報告されている

先天性LQTSの遺伝子診断率は60～70%であり，各遺伝子型の頻度は，LQT1が40%，LQT2が30～40%，LQT3が10%，LQT5とLQT6が2～5%，LQT4，LQT7については報告例だけである．LQT1とLQT5はI_{Ks}，LQT2とLQT6はI_{Kr}，LQT7はI_{K1}といずれもK^+電流の機能低下，LQT3はlate Na^+電流（I_{Na}）の機能亢進，LQT4は細胞内Ca^{2+}負荷により，いずれもQT時間が延長し，TdPを発症する．

遺伝子型による心事故の誘因の差異は交感神経刺激に対する反応の違いによる

LQT1型　交感神経刺激に対して最も感受性が強いタイプで，心事故（失神発作，蘇生に成功した心停止，突然死）の62%は運動中に起こる．また，水泳中の心事故はLQT1型に特徴的とされている．

LQT2型　心事故の43%は，情動ストレス（恐怖や驚愕），睡眠中の雑音（目覚まし時計など）による覚醒時などの急激に交感神経が緊張する状態で起こり，出産前後の心事故もLQT2型に特徴的とされている．

LQT3型　心事故の多くは睡眠中や安静時に多く，交感神経刺激が増悪因子とならないタイプである．

先天性LQTSでは浸透率は予想以上に低い

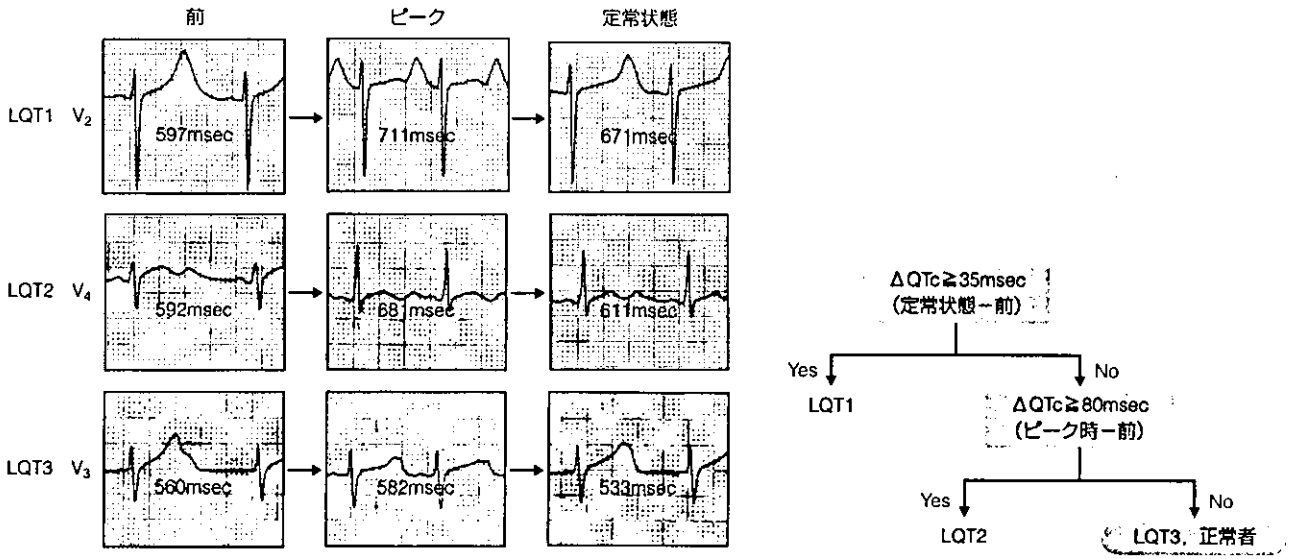
遺伝子診断率の向上により，先天性LQTSでは，遺伝子異常をもっていながら安静時のQT時間が正常範囲で失神などの発作の既往がなく，臨床的にはLQTSと診断されない，いわゆる非浸透患者（non-penetrant mutation carrier）が予想以上に多く存在することが明らかとなってきた（不完全浸透）．最近の著者らのデータでは，特にLQT1型で非浸透患者が多く，すなわち浸透率が低く（68%），LQT2型，LQT3型の浸透率はそれぞれ83%であった．言い換えれば，先天性LQTSの家族構成員で安静時のQT時間が正常であっても，そのなかには非浸透患者（潜在性LQTS）が存在する可能性がある．

エピネフリン負荷試験の実際

エピネフリン負荷試験は，末梢ラインを確保し，直流除細動器，インデラル®（塩酸プロプラノロール）をはじめとする緊急用薬品を準備したうえで，複数の医師の立会いのもとで行う．エピネフリンは0.1μg/kgのボーラス静注を行い，引き続き速やかに0.1μg/kg/分の持続点滴を施行する．12誘導心電図をエピネフリン投与前から連続記録し，QTcの計測は通常，エピネフリン投与前，エピネフリン投与後一過性に最も心拍数が上昇した時点（peak，エピネフリン開始から1～2分後），および心拍数が定常状態まで回復した時点（steady state，エピネフリン開始から3～4分後）で行う．特にLQT1型において意図せぬTdPの誘発を予防するために5分以上のエピネフリン点滴は避けるようにする．また，特に初回の負荷試験時には，緊張から内因性カテコラミンが誘発されやすいので，患者には負荷試験の目的，方法，心拍数が一過性に速くなることなどを十分に説明し，検査に対する不安を取り除くことが重要である．

遺伝子型別のエピネフリンに対するQTc時間の反応

LQT1，LQT2，LQT3型の各遺伝子型では，エピネフリン負荷に対するQTc時間の経時的反応が異なる（❶）．すなわち，LQT1患者では，



❶エピネフリン負荷に対する QTc 時間の経時的反応

❷エピネフリン負荷試験による遺伝子型の推定

エピネフリン開始直後に QTc 時間が著明に延長（平均約 130msec 延長）し，持続点滴中の定常状態でも QTc 時間延長が持続（約 80msec 延長）するのに対して，LQT2 患者では，エピネフリン開始直後には一過性に著明な QTc 時間延長（約130msec 延長）を認めるが，定常状態では QTc 時間はコントロールレベル近くまで短縮する．これに対して LQT3 患者では，エピネフリン開始直後の QTc 時間延長は軽度（約 35msec 延長）で，定常状態での QTc 時間はコントロールレベル以下に短縮する．

エピネフリン負荷試験による潜在性 LQTS の診断（非浸透患者の検出）

エピネフリン負荷試験は，特に LQT1 型で多いとされる潜在性 LQTS の診断，すなわち心電図による診断率の向上に有用である．著者らの成績では，エピネフリン点滴中の定常状態の QTc 時間を用いると，Keating の診断基準を用いた場合，LQT1 型の診断率は 68% から 87% へ，LQT2 型の診断率は 83% から 91% へと向上した．特異度はいずれも 100% であり，正常者で疑陽性になる（LQTS と誤って診断される）ことはなかった．LQT3 型では，エピネフリンにより QTc 時間は延長しないので，診断率は 83% のままであった．エピネフリン点滴中の peak の QTc 時間を用いると，LQT1，LQT2 型では診断率はさらに向上するが，特異度が低下するため，潜在性 LQTS の診断には，定常状態の QTc 時間を用いるのがよいと考えられる．

エピネフリン負荷試験による遺伝子型の推定

エピネフリン負荷試験は，また LQT1，LQT2，LQT3 型の遺伝子型の推定にも有用である（❷）．すなわち，エピネフリンに対する QTc 時間の経時的反応の違いから，定常状態で QTc 時間が 35msec 以上延長した場合は LQT1 型，定常状態の QTc 時間延長は 35msec 未満であるが，peak での QTc 時間延長が 80msec 以上の場合は LQT2 型，それ以外の場合は LQT3 型または正常者と推定される．エピネフリン負荷試験により遺伝子型が推定されれば，予測される遺伝子型からスクリーニングを行うことにより，遺伝子診断の経費や時間を節約することができる．実際，国立循環器病センターでは，エピネフリン負荷の反応から予想された遺伝子型の遺伝子を最初にダイレクトシークエンスすることにより，約 80% で遺伝子型が同定されている．また，原因遺伝子が同定されない先天性 LQTS 患者では，エピネフリン負荷に対する反応から治療方針を立てているのが現状である．

以上のように，エピネフリン負荷試験は，十分な準備と注意をはらったうえで施行すれば，潜在性 LQTS の診断（非浸透患者の検出）だけでなく，遺伝子型の推定にも有用であると考えられる．

Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome

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OBJECTIVES The aim of this study was to test the hypothesis that epinephrine test may have diagnostic value for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome (LQTS).

BACKGROUND A differential response of dynamic QT interval to epinephrine infusion between LQT1, LQT2, and LQT3 syndromes has been reported, indicating the potential diagnostic value of the epinephrine test for genotyping the three forms.

METHODS The responses of 12-lead ECG parameters to epinephrine were retrospectively examined in 15 LQT1, 10 LQT2, 8 LQT3, and 10 healthy volunteers to select the best ECG criteria for separating the four groups. The epinephrine test then was prospectively conducted in 42 probands clinically affected with LQTS, their 67 family members, and 10 new volunteers. The best criteria were applied in a blinded fashion to prospectively separate a different group of 31 LQT1, 23 LQT2, 6 LQT3, and 30 Control patients (10 genotype-negative LQT1, 10 genotype-negative LQT2 family members, and 10 volunteers).

RESULTS The sensitivity (penetrance) by ECG diagnostic criteria was lower in LQT1 (68%) than in LQT2 (83%) or LQT3 (83%) before epinephrine and was improved with steady-state epinephrine in LQT1 (87%) and LQT2 (91%) but not in LQT3 (83%), without the expense of specificity (100%). The sensitivity and specificity to differentiate LQT1 from LQT2 were 97% and 96%, those from LQT3 were 97% and 100%, and those from Control were 97% and 100%, respectively, when Δ mean corrected Q-Tend ≥35ms at steady state was used. The sensitivity and specificity to differentiate LQT2 from LQT3 or Control were 100% and 100%, respectively, when Δ mean corrected Q-Tend ≥80ms at peak was used.

CONCLUSIONS Epinephrine infusion is a powerful test to predict the genotype of LQT1, LQT2, and LQT3 syndromes as well as to improve the clinical diagnosis of genotype-positive patients, especially those with LQT1 syndrome.

KEYWORDS Arrhythmia; Diagnosis; Long QT syndrome; Catecholamines; Genes

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Table 1 Clinical characteristics of LQT1, LQT2, LQT3, and control groups in prospective study

	LQT1 (n = 31)	LQT2 (n = 23)	LQT3 (n = 6)	Control (n = 30)
Age [yr (range)]	21 ± 14 (4–55)	27 ± 16 (6–61)	21 ± 16 (7–43)	29 ± 15 (6–64)
Age <15 yr	16/31 (52%)	7/23 (30%)	3/6 (50%)	5/30 (17%)
Female sex	17/31 (55%)	16/23 (70%)	3/6 (50%)	16/30 (53%)
Baseline heart rate (beats/min)	67 ± 9	66 ± 12	60 ± 10	72 ± 13
Peak heart rate with Epi (beats/min)	99 ± 14	96 ± 16	95 ± 10	99 ± 13
Steady-state heart rate with Epi (beats/min)	85 ± 12	76 ± 14	70 ± 12	79 ± 13
Baseline QTc interval (ms)	470 ± 41†	503 ± 33*	506 ± 41*	408 ± 19
Syncope or aborted cardiac arrest	14/31 (45%)	12/23 (52%)	2/6 (33%)	(0%)
Beta-blockers	(0%)	(0%)	(0%)	(0%)

Values are given as mean ± SD where indicated.Epi = epinephrine; QTc = corrected QT.
*P < 0.05 vs LQT1 and control.
†P < 0.05 vs control.

The congenital long QT syndrome (LQTS) is a hereditary disorder caused by mutations in genes of the potassium and sodium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 17, and 21.[1–4] Among the LQT1, LQT2, and LQT3 forms, which account for approximately two thirds of genotyped patients, cardiac events are more often associated with sympathetic stimulation (physical or emotional stress) in LQT1 than in either LQT2 or LQT3 syndrome.[5–8] Concordant with the influence of sympathetic stimulation, beta-blockers are the most effective in LQT1 syndrome.[9,10] Therefore, genotyping of LQTS is of major importance because it would be helpful in managing and treating patients more effectively.[11] Preliminary studies by our and other groups have demonstrated the differential response of dynamic QT interval to epinephrine infusion between LQT1, LQT2, and LQT3 syndromes,[12,13] indicating the potential diagnostic value of the epinephrine test for genotyping the three forms. The present study was designed to test this hypothesis.

Methods

Study design and population

First, we retrospectively analyzed the response of ECG parameters to epinephrine infusion in 15 LQT1 patients (5 families), 10 LQT2 patients (5 families), 8 LQT3 patients (2 families), and 10 healthy volunteers (Control), some of whom were included in our previous study.[12] The best ECG criteria separating LQT1, LQT2, LQT3, and Control patients were selected. Then, we prospectively conducted an epinephrine test in 42 probands who were clinically diagnosed as having congenital LQTS, their 67 family members, and 10 new healthy volunteers. The best ECG criteria with the epinephrine test derived from the retrospective study were applied in a blinded fashion to differentiate LQT1, LQT2, LQT3, and Control groups in a total of 119 subjects. Molecular screening, which was performed after the epinephrine test, identified 31 genotype-positive LQT1 patients (12 families), 23 genotype-positive LQT2 patients (12 families), 6 genotype-positive LQT3 patients (3 families), 10 genotype-negative LQT1 patients (9 families), and 10 genotype-negative LQT2 patients (4 families). The study population of the prospective study included the 31 LQT1, 23 LQT2, and 6 LQT3 patients. The data from the 10 genotype-negative LQT1 patients, 10 genotype-negative LQT2 patients, and 10 healthy volunteers were pooled and referred to as Control group, because there were no significant differences in the clinical and ECG characteristics among the three groups. In the remaining 29 patients including 15 probands (15 families), no responsible mutations were identified in any LQTS genes. There were no significant differences among LQT1, LQT2, LQT3, and Control groups with regard to age, percentage of age <15 years old, gender, baseline heart rate, and peak and steady-state heart rate with epinephrine in the prospective study (Table 1). Percentage of syncope or aborted cardiac arrest was no different among LQT1, LQT2, and LQT3 groups (Table 1). The baseline corrected QT intervals in LQT2 and LQT3 groups were significantly longer than that in the LQT1 group; those in the LQT1, LQT2, and LQT3 groups were all significantly longer than that in the Control group (Table 1). Genotyping of LQTS was reviewed and approved by our Ethical Review Committee, and written informed consent was obtained from all patients or their parents when the patients were younger than 20 years. All epinephrine tests were conducted in the National Cardiovascular Center as part of a clinical

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evaluation of LQTS patients. We previously reported that the oral beta-blocker propranolol (0.5–2 mg/kg) completely suppressed the effects of epinephrine on repolarization parameters[14]; therefore, no subjects took beta-blockers at the time of the epinephrine test in either the retrospective or prospective study. Among a total of 93 genotyped LQTS patients in the retrospective and prospective studies, 85 patients were transferred to our hospital for initial evaluation of LQTS without any medications including beta-blockers, and the epinephrine test could be conducted in the absence of beta-blockers. Appropriate therapies, including beta-blockers, were started after the evaluation of LQTS. In the remaining 8 patients (3 LQT1 and 5 LQT2), beta-blockers were withheld during the evaluation of LQTS, including the epinephrine test, and then reinstated.

Clinical diagnosis

LQTS-affected individuals were diagnosed based on the ECG criteria of Keating et al,[15] including a corrected QT ≥470 ms in asymptomatic individuals and a corrected QT >440 ms for males and >460 ms for females associated with ≥1 of the following: (1) stress-related syncope, (2) documented torsades de pointes, or (3) family history of early sudden cardiac death. The LQTS score was calculated using the diagnostic criteria of Schwartz et al.[16]

Recording of standard 12-lead ECG

A standard 12-lead ECG was recorded using an FDX6521 (Fukuda Denshi Co., Tokyo, Japan) with the patient in the supine position. These ECG data were digitized using analog-to-digital converters at a sampling rate of 1,000 samples per second per channel.

Measurements

Measurement of the ECG parameters was performed against five averaged QRS complexes by an off-line computer with an analysis program developed by our institution. Q-Tend was defined as the interval between QRS onset and the point at which an isoelectric line intersected a tangential line drawn at the minimum dV/dt point of a positive T wave or at the maximum dV/dt point of a negative T wave. When a bifurcated or secondary T wave (pathologic U wave) appeared, it was included as part of the measurement of the Q-Tend, but a normal U wave, which was apparently separated from a T wave, was not included. Q-Tpeak was defined as the interval between QRS onset and the peak of the positive T wave or the nadir of the negative T wave. When the T wave had a biphasic or a notched configuration, the peak of the T wave was defined as that of dominant T deflection. Q-Tend, Q-Tpeak, and Tpeak-end (Q-Tend − Q-Tpeak) as an index of transmural dispersion of repolarization were measured automatically from all 12-lead ECGs, corrected by Bazett's method, and averaged among all 12 leads. Data of corrected Q-Tend, Q-Tpeak, and Tpeak-end, which were measured simply from lead V_5, also were evaluated. As an index of spatial dispersion of repolarization, dispersion of the corrected Q-Tend was defined as the interval between the maximum and the minimum of the corrected Q-Tend among the 12 leads.

Epinephrine administration

A bolus injection of epinephrine (0.1 μg/kg) was immediately followed by continuous infusion (0.1 μg/kg/min). The 12-lead ECG was continuously recorded during sinus rhythm under baseline conditions and usually for 5 minutes under epinephrine infusion. The effect of epinephrine on both RR and QT intervals usually reached steady-state conditions 2 to 3 minutes after the start of epinephrine infusion. Epinephrine infusion for >5 minutes was avoided, and ECG monitoring was continued for another 5 minutes after epinephrine infusion to detect the possible occurrence of torsades de pointes. The ECG data as a representative of the peak epinephrine effect were collected 1 to 2 minutes after the start of epinephrine infusion when the RR interval was the shortest, whereas the data as a representative of the steady-state epinephrine effect were collected 3 to 5 minutes after the start of epinephrine infusion.

Statistical analysis

Data are expressed as mean ± SD, except for those shown in Figure 3, which are expressed as mean ± SEM. Repeated-measures two-way ANOVA followed by the Scheffé test was used to compare measurements made before and after epinephrine infusion and to compare differences between groups (STATISTICA, 98 Edition). Repeated-measures one-way ANOVA followed by the Scheffé test was used to compare changes (Δ) in the measurements with epinephrine between groups. Differences in frequencies were analyzed by Chi-square test. A two-sided $P < .05$ was considered statistically significant.

Results

Retrospective study

Best ECG criteria to differentiate LQT1, LQT2, LQT3, and Control groups

The retrospective study as well as our previous study[12] suggested the differential response of the mean corrected Q-Tend interval to epinephrine test among LQT1, LQT2, and LQT3 groups. The mean corrected Q-Tend intervals were more prominently prolonged at peak epinephrine effect in LQT1 and LQT2 groups than in either the LQT3 or the Control group. On the other hand, they remained pro-

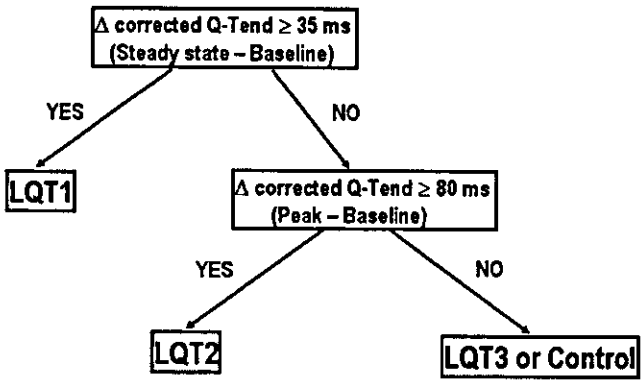

Figure 1 Flow chart for predicting genotype with the epinephrine test.

longed at steady-state epinephrine effect only in the LQT1 group but not in the other three groups.

Figure 1 illustrates a flow chart for predicting LQT1, LQT2, LQT3, and Control patients with the epinephrine test derived from the retrospective study. If the Δ mean corrected Q-Tend was ≥35 ms at steady-state epinephrine effect, the patient was expected to be affected with LQT1 syndrome. If not, and the Δ mean corrected Q-Tend was ≥80 ms at peak epinephrine effect, the patient was expected to be linked to LQT2 syndrome. If not, the patient was expected to be an LQT3 or Control patient.

Prospective study

Differential responses of ECG parameters to epinephrine infusion

Figure 2 illustrates ECG lead V_4 under baseline conditions and at peak and steady-state epinephrine effects in representative LQT1, LQT2, LQT3, and Control patients.

Figure 3 shows composite data of the ECG parameters under baseline conditions and at peak and steady-state epinephrine effects in the four groups of the prospective study. Under baseline conditions, the mean corrected Q-Tend and Q-Tpeak were significantly longer in the LQT1, LQT2, and LQT3 groups than in the Control group; both were significantly longer in the LQT2 and LQT3 groups than in LQT1 group (Figure 3A and 3B). The mean corrected Tpeak-end was significantly greater in the LQT2 group than in the LQT3 or Control group (Figure 3C). The dispersion of corrected Q-Tend was significantly larger in the LQT1 and LQT2 groups than in the Control group (Figure 3D). The mean corrected Q-Tend and Q-Tpeak were dramatically prolonged at peak epinephrine effect (470 ± 41 to 596 ± 56 ms, 385 ± 34 to 480 ± 53 ms; $P < .05$, respectively) and remained prolonged at steady state (549 ± 55 ms, 438 ± 50 ms; $P < .05$ vs baseline, respectively) in the LQT1 group (Figure 3A and 3B, closed circles). The mean corrected Tpeak-end also was markedly increased at peak epinephrine effect (85 ± 11 to 115 ± 19 ms; $P < .05$), and remained increased at steady state (111 ± 17 ms; $P < .05$ vs baseline) as a result of a greater prolongation in the mean corrected

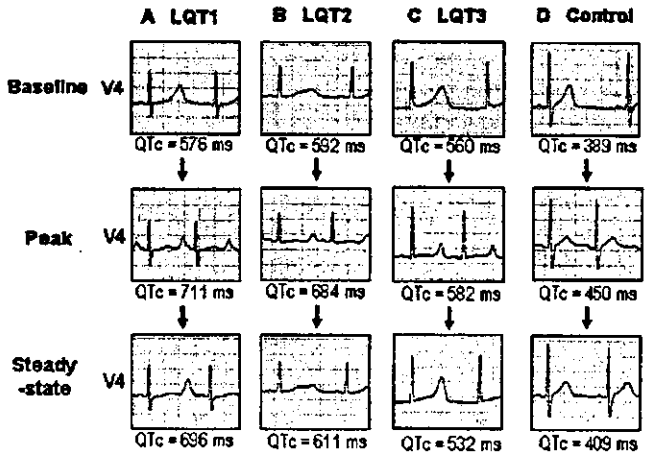

Figure 2 ECG lead V_4 under baseline conditions and at peak and steady-state epinephrine effects in LQT1 (**A**), LQT2 (**B**), LQT3 (**C**), and Control (**D**) patients. The mean corrected Q-Tend was prominently prolonged from 576 to 711 ms at peak epinephrine effect and remained prolonged at steady state (696 ms) in the LQT1 patient. In the LQT2 patient, the mean corrected Q-Tend also was dramatically prolonged from 592 to 684 ms at peak but returned to the baseline level at steady-state (611 ms). It was much less prolonged (LQT3: 560 to 582 ms, Control: 389 to 450 ms) at peak in the LQT3 and Control patients than in either the LQT1 or LQT2 patient and was shortened to the baseline level at steady state (532, 409 ms).

Q-Tend than in the mean corrected Q-Tpeak at both peak and steady-state conditions (Figure 3C, closed circles). The mean corrected Q-Tend and Q-Tpeak also were dramati-

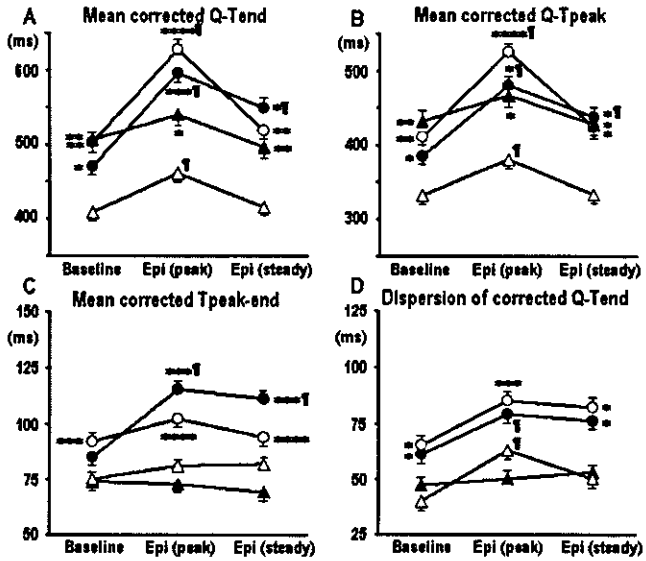

Figure 3 Composite data of the mean corrected Q-Tend (**A**), Q-Tpeak (**B**), Tpeak-end (**C**), and dispersion of corrected Q-Tend (**D**) under baseline conditions and at peak and steady-state epinephrine effects in LQT1 *(closed circle)*, LQT2 *(open circle)*, LQT3 *(closed triangle)*, and Control *(open triangle)* groups of the prospective study. *$P < .05$ vs Control; **$P < .05$ vs LQT1 and Control; ***$P < .05$ vs LQT3 and Control; ****$P < .05$ vs LQT1, LQT3, and Control; ¶$P < .05$ vs baseline.

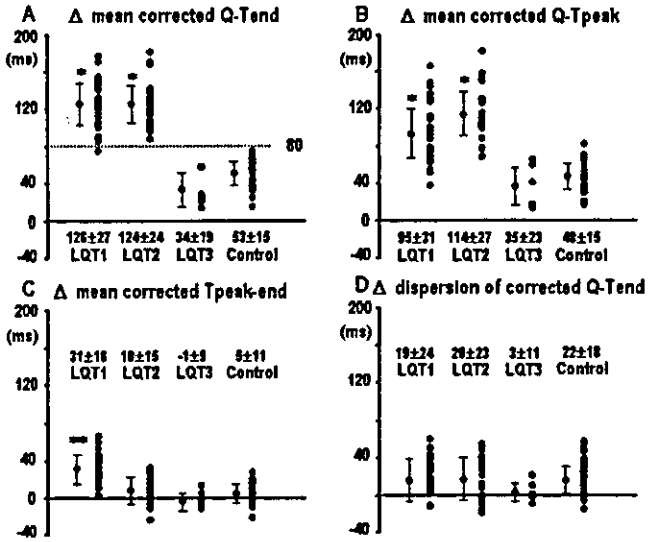

Figure 4 Composite data of changes (Δ) in the mean corrected Q-Tend (**A**), Q-Tpeak (**B**), Tpeak-end (**C**), and dispersion of corrected Q-Tend (**D**) between baseline conditions and peak epinephrine effects in LQT1, LQT2, LQT3, and Control groups of the prospective study. *$P < .05$ vs LQT3 and Control; **$P < .05$ vs LQT2, LQT3 and Control.

cally prolonged at peak epinephrine effect (503 ± 33 to 627 ± 30 ms, 411 ± 26 to 525 ± 32 ms; $P < .05$, respectively) in the LQT2 group but returned to baseline levels at steady state (518 ± 38 ms, 424 ± 36 ms; P = NS vs baseline, respectively; Figure 3A and 3B, open circles). The mean corrected Tpeak-end was unchanged with epinephrine (92 ± 23 to 102 ± 18 to 94 ± 19 ms) in the LQT2 group (Figure 3C, open circles). The mean corrected Q-Tend and Q-Tpeak were much less prolonged at peak epinephrine effect (LQT3: 506 ± 41 to 540 ± 28 ms; P = NS, 432 ± 40 to 467 ± 26 ms; P = NS, Control: 408 ± 19 to 461 ± 19 ms, 332 ± 17 to 380 ± 23 ms; $P < .05$, respectively) in the LQT3 and Control groups than in the LQT1 or LQT2 group and were shortened to the baseline levels at steady state (LQT3: 496 ± 37 ms, 427 ± 30 ms; Control: 415 ± 18 ms, 333 ± 19 ms; P = NS vs baseline, respectively) (Figure 3A and 3B, closed triangles and open triangles). The mean corrected Tpeak-end was unchanged with epinephrine (LQT3: 74 ± 7 to 73 ± 4 to 69 ± 10 ms; Control: 75 ± 8 to 81 ± 13 to 82 ± 11 ms) in the LQT3 and Control groups (Figure 3C, closed triangles and open triangles). The dispersion of corrected Q-Tend was increased at peak epinephrine effect in the LQT1 and Control groups (LQT1: 61 ± 21 ms, 79 ± 27 ms; Control: 40 ± 14 ms, 63 ± 19 ms; $P < .05$, respectively).

Figure 4 illustrates the changes (Δ) in the ECG parameters between baseline conditions and peak epinephrine effects in the four groups of the prospective study. Both the Δ mean corrected Q-Tend and Q-Tpeak were no different between the LQT1 and LQT2 groups, but they were significantly greater than those in the LQT3 and Control groups ($P < .05$; Figure 4A and 4B). No significant differences were observed in the Δ mean corrected Q-Tend and Q-Tpeak between the LQT3 and Control groups. The Δ mean corrected Tpeak-end was significantly greater in the LQT1 group than in the other three groups ($P < .05$; Figure 4C). No significant differences were observed in the Δ dispersion of corrected Q-Tend among the four groups (Figure 4D). As suggested by the retrospective study, the Δ mean corrected Q-Tend ≥80 ms at peak epinephrine effect could most effectively differentiate the LQT1 and LQT2 groups from the LQT3 or Control group (Figure 4A).

Figure 5 illustrates Δ in the ECG parameters between baseline conditions and steady-state epinephrine effects in the four groups of the prospective study. The Δ mean corrected Q-Tend, Q-Tpeak, and Tpeak-end were significantly greater in LQT1 than in the other three groups ($P <$ .05; Figure 5A–5C). The Δ mean corrected Q-Tend was significantly larger in the LQT2 than in LQT3 group ($P <$ .05; Figure 5A). There were no significant differences in the Δ dispersion of corrected Q-Tend among the four groups (Figure 5D). As suggested by the retrospective study, the Δ mean corrected Q-Tend ≥35 ms at steady-state epinephrine effect could most effectively differentiate the LQT1 group from the other three groups (Figure 5A).

Improvement of clinical diagnosis with epinephrine test

The sensitivity (i.e., penetrance) and specificity for identifying genotype-positive LQT1, LQT2, and LQT3 patients by the ECG diagnostic criteria before and after steady-state epinephrine effects were evaluated in the prospective study.

The sensitivity for identifying genotype-positive LQT1 patients among the LQT1 and Control groups was low under baseline conditions; 68% (21/31) using the ECG

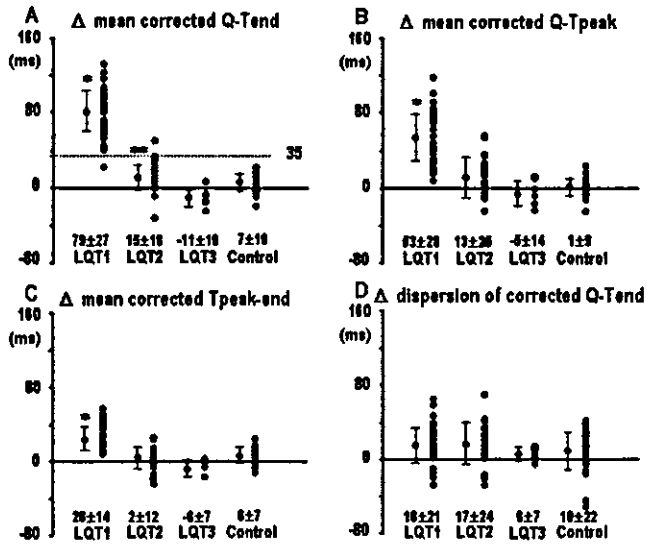

Figure 5 Composite data of changes (Δ) in the mean corrected Q-Tend (**A**), Q-Tpeak (**B**), Tpeak-end (**C**), and dispersion of corrected Q-Tend (**D**) between baseline conditions and steady-state epinephrine effects in LQT1, LQT2, LQT3 and Control groups of the prospective study. *$P < .05$ vs LQT2, LQT3 and Control; **$P < .05$ vs LQT3.

Table 2 Prediction of genotype with the epinephrine test in prospective study

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
LQT1 vs LQT2	97%	96%	97%	96%	96%
Δ Mean corrected Q-Tend ≥35 ms (Steady state-Baseline)	(90%)	(83%)	(88%)	(86%)	(87%)
LQT1 vs LQT3	97%	100%	100%	86%	97%
Δ Mean corrected Q-Tend ≥35 ms (Steady state-Baseline)	(90%)	(100%)	(100%)	(67%)	(92%)
LQT1 vs control	97%	100%	100%	97%	98%
Δ Mean corrected Q-Tend ≥35 ms (Steady state-Baseline)	(90%)	(97%)	(97%)	(91%)	(93%)
LQT2 vs LQT3	100%	100%	100%	100%	100%
Δ Mean corrected Q-Tend ≥80 ms (Peak-Baseline)	(91%)	(100%)	(100%)	(75%)	(93%)
LQT2 vs control	100%	100%	100%	100%	100%
Δ Mean corrected Q-Tend ≥80 ms (Peak-Baseline)	(91%)	(90%)	(88%)	(93%)	(91%)

Percentages in parentheses indicate those calculated by data measured simply from ECG lead V_5. Δ-Increase with epinephrine.

diagnostic criteria, 68% (21/31) when an LQTS score ≥4 was used, and 74% (23/31) when a score ≥2 was used. The specificity was 100% (30/30) regardless of the criteria. The sensitivity was substantially improved by measurement of the mean corrected Q-Tend at steady-state epinephrine effect without the expense of specificity (100% [30/30]); 87% (27/31), 81% (25/31), and 90% (28/31), respectively.

The sensitivity for identifying genotype-positive LQT2 patients among the LQT2 and Control groups was relatively high under baseline conditions; 83% (19/23), 83% (19/23), and 96% (22/23), respectively. The sensitivity was further improved at steady-state epinephrine effect to 91% (21/23), 91% (21/23), and 96% (22/23), respectively, without the expense of specificity (100% [30/30]).

The sensitivity for identifying genotype-positive LQT3 patients among the LQT3 and Control groups under baseline conditions was 83% (5/6), 50% (3/6), and 100% (6/6), respectively, which was unchanged at steady-state epinephrine effect by any of the three criteria.

Prediction of genotype with epinephrine test

Table 2 illustrates the predictive values with the epinephrine test for genotyping in the prospective study. The Δ mean corrected Q-Tend ≥35 ms at steady-state epinephrine effect could differentiate LQT1 from the LQT2, LQT3, or Control group with predictive accuracy ≥90%. The Δ mean corrected Q-Tend ≥80 ms at peak epinephrine effect could differentiate LQT2 from LQT3 or Control group with predictive accuracy of 100%. Even if we calculated the predictive values by the Δ corrected Q-Tend, which was measured simply from ECG lead V_5, the predictive accuracy still was high (≥80%).

At molecular screening, the responsible mutations could be identified in the first targeted gene suspected by the epinephrine test in all of the 12 LQT1, 12 LQT2, and 3 LQT3 families of the prospective study.

Response to epinephrine test in genotype-unknown patients

Figure 6 illustrates Δ mean corrected Q-Tend at peak (Figure 6A) and steady-state (Figure 6B) epinephrine effects in the 29 patients (15 probands and 14 family members) of the prospective study in whom the responsible mutations could not be identified in any LQTS genes. Among the 15 probands, the response to the epinephrine test was LQT1 pattern in 11 probands and LQT2 pattern in 4 probands. Among the 14 family members, the response was LQT1 pattern in 3 members, LQT2 pattern in 3 members, and LQT3 or Control pattern in 8 members. Even though these 29 patients without causative mutations were included in the analysis for genotype prediction, the positive predictive values were 67% (30/31+14) for LQT1 syndrome and 73% (22/23+7) for LQT2 syndrome, respectively.

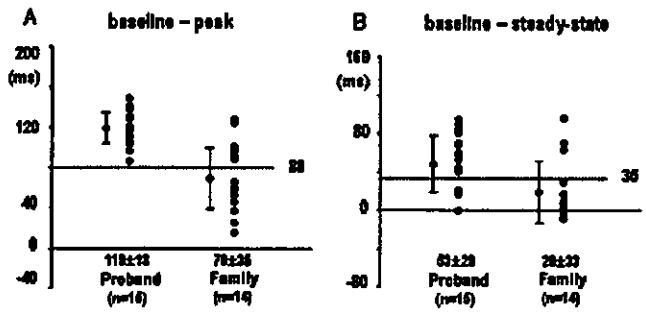

Figure 6 Composite data of changes (Δ) in the mean corrected Q-Tend between baseline conditions and peak epinephrine effects (**A**) and between baseline conditions and steady-state epinephrine effects (**B**) in the 29 patients (15 probands and 14 family members) of the prospective study in whom the responsible mutations could not be identified in any LQTS genes.

Complications

Spontaneously terminating torsades de pointes was induced by epinephrine infusion in one LQT1 patient, and spontaneous premature ventricular contractions were induced in one LQT1 and two LQT2 patients.

Discussion

The main findings of the present study are as follows: (1) penetrance in the absence of sympathetic stimulation was lower in LQT1 than in LQT2 or LQT3 syndrome and was improved with steady-state epinephrine in LQT1 and LQT2, but not in LQT3 syndromes; and (2) epinephrine infusion was a powerful test to predict the genotype of LQT1, LQT2, and LQT3 syndromes by comparing the Δ corrected Q-Tend at peak and steady-state epinephrine effects.

Penetrance in LQT1, LQT2, and LQT3 syndromes

It has long been expected that all genotype-positive patients could not be diagnosed by using ECG diagnostic criteria.[17,18] Priori et al[19] conducted molecular screening in nine families with sporadic cases of LQTS and suggested that clinical diagnostic criteria had low sensitivity (penetrance; 38%) in identifying mutation carriers. Swan et al[20] reported that the sensitivity and specificity for identifying genotype-positive patients were 53 and 100%, respectively, in a LQT1 family (D188N). Similarly, in the 12 LQT1 families of the prospective study, the sensitivity for identifying LQT1 patients was low under baseline conditions and was substantially improved with the epinephrine test without the expense of specificity. In contrast, the sensitivity for identifying LQT2 and LQT3 patients was relatively high under baseline conditions in the 12 LQT2 and 3 LQT3 families. These findings suggest the need for molecular screening of all family members regardless of clinical diagnosis to confirm genotype-positive patients, especially in LQT1 syndrome.

Epinephrine test for predicting genotype of LQT1, LQT2, and LQT3 syndromes

Recent clinical data on genotype-phenotype correlation and experimental data in LQTS models have demonstrated the genotype-specific response to sympathetic stimulation and the possibility of genotype-specific therapy.[5–8,11–14,21–23] The LQT1, LQT2, and LQT3 syndromes constitute approximately two thirds of genotyped LQTS patients.[24] Therefore, genotyping of the three forms as well as identifying latent genotype-positive patients are of particular importance in the management and treatment of LQTS patients. Because molecular diagnosis still is unavailable to many institutes, is costly, and is time consuming, genotype identification by clinical tests would be useful for stratifying molecular screening by targeting suspected genes for an initial study.[25–28] Moreover, there are still 30% to 40% of patients clinically affected with LQTS in whom no responsible mutations can be identified. Therefore, it is of great importance to diagnose, based on clinical findings, the form of LQTS that patients are affected with.

Our data demonstrate that epinephrine infusion enables us to predict the genotype of LQT1, LQT2, and LQT3 syndromes as well as to improve the clinical diagnosis of genotype-positive patients, especially in LQT1 syndrome. Genotype prediction of the three syndromes by the epinephrine test would facilitate molecular screening by targeting suspected genes. In fact, molecular screening identified the responsible mutations in the first targeted gene suspected by the epinephrine test in all of the 12 LQT1, 12 LQT2, and 3 LQT3 families of the prospective study. On the other hand, the other 15 probands were assigned to a likely genotype by the epinephrine test, but no mutations were found in any LQTS genes. Because the response to the epinephrine test was LQT1 (11 probands and 3 family members) or LQT2 pattern (4 probands and 3 family members), some ion channel or membrane adapter genes, which are sensitive to catecholamines, may be candidates for responsible genes. It is noteworthy that the positive predictive values for LQT1 and LQT2 syndromes still were high (67% for LQT1 and 73% for LQT2), even though the 29 patients without responsible mutations in any LQTS genes were included in the analysis for genotype prediction. The genotype prediction also may help to stratify the management and treatment of LQTS patients, if the patients cannot be genotyped by the molecular screening.

Conclusion

Epinephrine infusion is a powerful test to predict the genotype of LQT1, LQT2, and LQT3 syndromes as well as to improve the clinical diagnosis of genotype-positive patients, especially in LQT1 syndrome.

Acknowledgments

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Mutation Site-Specific Differences in Arrhythmic Risk and Sensitivity to Sympathetic Stimulation in the LQT1 Form of Congenital Long QT Syndrome

Multicenter Study in Japan

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OBJECTIVES We sought to compare the arrhythmic risk and sensitivity to sympathetic stimulation of mutations located in transmembrane regions and C-terminal regions of the *KCNQ1* channel in the LQT1 form of congenital long QT syndrome (LQTS).

BACKGROUND The LQT1 syndrome is frequently manifested with variable expressivity and incomplete penetrance and is much more sensitive to sympathetic stimulation than the other forms.

METHODS Sixty-six LQT1 patients (27 families) with a total of 19 transmembrane mutations and 29 patients (10 families) with 8 C-terminal mutations were enrolled from five Japanese institutes.

RESULTS Patients with transmembrane mutations were more frequently affected based on electrocardiographic (ECG) diagnostic criteria (82% vs. 24%, $p < 0.0001$) and had more frequent LQTS-related cardiac events (all cardiac events: 55% vs. 21%, $p = 0.002$; syncope: 55% vs. 21%, $p = 0.002$; aborted cardiac arrest or unexpected sudden cardiac death: 15% vs. 0%, $p = 0.03$) than those with C-terminal mutations. Patients with transmembrane mutations had a greater risk of first cardiac events occurring at an earlier age, with a hazard ratio of 3.4 ($p = 0.006$) and with an 8% increase in risk per 10-ms increase in corrected Q-Tend. The baseline ECG parameters, including Q-Tend, Q-Tpeak, and Tpeak-end intervals, were significantly greater in patients with transmembrane mutations than in those with C-terminal mutations ($p < 0.005$). Moreover, the corrected Q-Tend and Tpeak-end were more prominently increased with exercise in patients with transmembrane mutations ($p < 0.005$).

CONCLUSIONS In this multicenter Japanese population, LQT1 patients with transmembrane mutations are at higher risk of congenital LQTS-related cardiac events and have greater sensitivity to sympathetic stimulation, as compared with patients with C-terminal mutations. (J Am Coll Cardiol 2004;44:117–25) © 2004 by the American College of Cardiology Foundation

Congenital long QT syndrome (LQTS) is a hereditary disorder characterized by a prolonged QT interval on the electrocardiogram (ECG), commonly associated with polymorphic ventricular tachycardia known as torsade de pointes (TdP), often leading to severe symptoms, such as syncope and sudden cardiac death (1,2). Genetic studies have so far identified seven forms of congenital LQTS caused by mutations in genes of the potassium and sodium channels or the membrane adapter located on chromosomes 3, 4, 7, 11, 17, and 21 (3–5). Among the seven forms, LQT1 syndrome is one of the two most common genetic variants of LQTS and accounts for approximately 25% of genotyped patients (6). Mutations in *KCNQ1* are responsible for defects in the slowly activating component of the delayed rectifier potassium current (I_{Ks}) underlying LQT1 syndrome (7). The LQT1 syndrome is frequently manifested with variable expressivity and incomplete penetrance (8–10) and is much more sensitive to sympathetic stimulation than the other forms (11,12).

Examination of the genotype-phenotype correlation is important for the management and treatment of patients with congenital LQTS, especially in the LQT1, LQT2, and LQT3 forms, which constitute approximately two-thirds of genotyped LQTS (13). More recently, mutation site-specific differences in the severity of phenotype have been

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