Role of Signal-Averaged ECG in Predicting Results of Flecainide Provocation Test Used in Family Screening for Brugada Syndrome

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MOK ET AL.: ***Role of Signal-Averaged ECG in Predicting Results of Flecainide Provocation Test Used in Family Screening for Brugada Syndrome.*** *Brugada syndrome (BS) is an inherited arrhythmogenic disease with an autosomal dominant mode of inheritance. Flecainide provocation test (FPT) has been shown to be highly sensitive and specific in unmasking the Brugada ECG pattern in affected subjects. We sought to test if late potential (LP) in signal-averaged electrocardiogram (SAECG) is helpful in predicting the results of FPT used in family screening for BS. The study included 17 asymptomatic Chinese subjects from 8 families (M:F 10:7, mean age 24.8±11.4 years) who have undergone family screening for BS. All screened subjects had a normal 12-lead ECG at baseline. None had structural heart disease. SAECG using a time domain analysis was recorded prior to the FPT. LP is defined as positive when at least 2 of the 3 criteria are met: (1) filtered QRS duration >114ms; (2) root-mean square voltage of terminal 40ms of QRS ≦20μV; (3) low-averaged signal <40μV of terminal QRS ≧38ms. Seven subjects had a positive LP on SAECG. Among them 3 had a positive FPT. As for the 10 subjects with a negative LP, none had a positive FPT. Thus in predicting the results of FPT among these subjects, LP on SAECG has a sensitivity, specificity, positive predictive value and negative predictive value of 100%, 76.9%, 42.8% and 100% respectively.* ***Conclusion:*** *LP on SAECG has a high sensitivity and negative predictive value in predicting results of FPT used in family screening for BS. (J HK Coll Cardiol 2002;10:105-108)*

Brugada syndrome, flecainide, signal-averaged electrocardiography, ST-segment elevation

摘要

Brugada 綜合征（BS）是一個遺傳性心律失常性疾病，伴有一個常染色體顯性遺傳模式。氟卡尼激發試驗（FPT）在顯露受累個體 Brugada ECG 波形方面有著很高的敏感性和特異性。我們試圖檢驗單信號平均 ECG（SAECG）中的晚電位（LP）是否有助於預測應用于家族篩查 BS 的 FPT 試驗結果。該研究包括 17 例已進行家族 BS 篩查的來自於 8 個中國家庭的無症狀個體（M:F 10:7，平均年齡 24.8±11.4 歲）。所有篩查的個體均有正常的基礎 12 導聯心電圖。均無器質性心臟病。SAECG 應用時域分析並在 FPT 前進行記錄。LP 陽性被定義為至少滿足下列 3 個條件中的 2 個（1）濾波的 QRS 間期大於 114 毫秒（2）濾波疊加後 QRS 終末 40 ms 振幅的均方根 ≤20 μV（3）QRS 終末部振幅低於 40 μV的時間≧38 毫秒。7 位元個體 SAECG 顯示 LP 陽性。其中 3 個 FPT 陽性。另 10 位 LP 陰性，FPT 均陰性。在這些個體中預測 FPT 試驗結果，SAECG 中 LP 的敏感性、特異性、陽性預測值和陰性預測值分別為 100%、76.9%、42.8%和 100%。結論：SAECG 中的 LP 在預測用於家族篩查 BS 的 FPT 結果方面有著較高的敏感性和陰性預測值。

關鍵詞：Brugada 綜合征　氟卡尼　單信號平均 ECG　ST 段抬高

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Introduction

Brugada syndrome is a genetically determined primary electrical disease characterized by a marked ST-segment elevation in leads V_1-V_3 on electrocardiogram (ECG) during sinus rhythm and a propensity for life-threatening ventricular tachy-arrhythmias.[1] Flecainide provocation test (FPT) has been shown to be highly sensitive and specific in unmasking the Brugada ECG pattern in subjects with a concealed form of the disease[2] and therefore frequently used in family screening for the syndrome. Late potential on signal-averaged electrocardiogram (SAECG) is frequently recorded in patients with Brugada syndrome[3] but only rarely found among healthy subjects. We therefore sought to study if SAECG is helpful in predicting the results of FPT used in family screening for Brugada syndrome in our local Chinese population.

Methods

In Princess Margaret Hospital (PMH), FPT has been used to identify Brugada syndrome among family members of symptomatic patients with the syndrome if their baseline ECG is normal or non-diagnostic. SAECG using a time domain analysis is recorded and echocardiogram performed. This is followed by a FPT if no structural heart disease is found on echocardiogram. LP is defined as positive when at least 2 of the 3 criteria are met: (1) filtered QRS duration >114 ms; (2) root-mean square voltage of terminal 40 ms of QRS $\leqq$20 μV; (3) low-averaged signal <40 μV of terminal QRS $\geqq$38 ms. After an informed consent is obtained, FPT is performed in Cardiac Care Unit under continuous cardiac monitoring. Flecainide at a dosage of 2 mg/kg (maximum 150 mg) is given intravenously over 10 minutes. Leads V_1 and V_2 are recorded in the 2nd and 3rd intercostal spaces in addition to the conventional 4th intercostal space which has been shown to enhance the sensitivity of FPT.[4] A positive FPT is defined as occurrence of terminal R wave and >1 mm ST segment elevation in leads V_1-V_3 following flecainide infusion. Subjects with a positive FPT will be monitored for 6 hours or until the ST segment in leads V_1-V_3 returns to baseline. Sensitivity, specificity, positive and negative predictive values of SAECG in predicting the results of FPT are calculated.

Results

From February 1999 to December 2001, a total of 17 asymptomatic Chinese subjects (M:F 10:7) with a mean age of 24.8±11.4 years have undergone family screening for Brugada syndrome in PMH. They came from 8 families. Each family had one proband member suffering from Brugada syndrome (Ventricular fibrillation in 5, recurrent syncope in 2 and asymptomatic in 1). All 17 subjects had a normal 12-lead ECG at baseline. None had structural heart disease found on echocardiogram. Of these 17 subjects, 7 had a positive LP on SAECG. Among these 7 subjects 3 had a positive FPT (Figure 1A) while 4 had a negative FPT. Among the 10 subjects with a negative LP, none had a positive FPT (Figure 1B). Thus in predicting the results of FPT among these subjects, LP on SAECG has a sensitivity, specificity, positive predictive value and negative predictive value of 100%, 76.9%, 42.8% & 100% respectively. Two subjects complained of dizziness during flecainide infusion which rapidly subsided upon completion of the test. Transient unifocal ventricular premature beats were recorded in 1 subject. No bradyarrhythmia or tachyarrhythmia was found in any subject during FPT.

Discussion

Brugada syndrome is potentially life-threatening disease. Symptomatic patients may have up to a 62% chance of arrhythmia recurrence over a 4-year follow-up.[5] As this syndrome is an inherited disease with an autosomal dominant mode of inheritance, it is therefore essential to screen their family members who may also be affected and therefore predisposed to life-threatening ventricular arrhythmias. Genetic data has linked this syndrome to mutations in cardiac sodium channel gene SCN5A in chromosome 3.[6,7] However SCN5A mutation can be found in only 15-25% of patients with this syndrome.[8] Genetic screening for SCN5A mutation is therefore an insensitive test in family screening to identify Brugada syndrome unless SCN5A mutation is

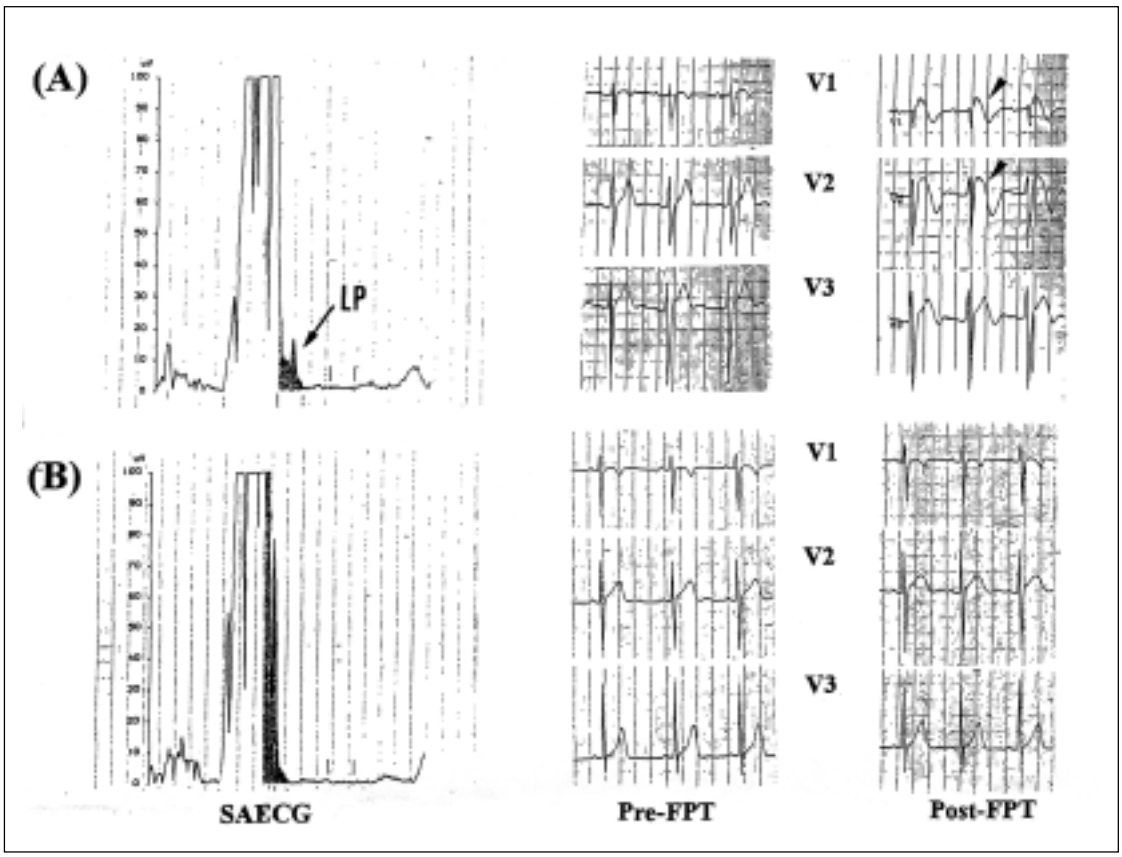

Figure 1. *Late potential (LP) on signal-averaged ECG (SAECG) predicting results of flecainide provocation test (FPT) in family screening for Brugada syndrome (see text). (A) Positive FPT evidenced by coved type ST-segment elevation (arrowheads) in leads V_1-V_2 following flecainide infusion in a subject with a positive LP on SAECG (B) Negative FPT in a subject with a negative LP on SAECG.*

already documented in probands. Moreover, genetic test for channelopathies is expensive and not easily accessible. Using 12-lead ECG to diagnose Brugada syndrome among family members is easy if the typical Brugada ECG pattern is found on their ECG during sinus rhythm. However, dynamic changes or transient normalization of the ST-segment may obscure the correct diagnosis. Flecainide, a potent sodium channel blocker, has been shown to be highly sensitive and specific in unmasking the syndrome in affected subjects who have normal baseline ECG.[2] It is therefore frequently used locally[9] and world-wide for the purpose of family screening in Brugada syndrome.

LP on SAECG reflects conduction delay in the ventricles. Although at present the role of conduction disturbance in the right ventricle in arrhythmogenesis of the syndrome is a matter of some controversy, it is well known that LP on SAECG is frequently found in patients suffering from Brugada syndrome.[3] LP can be found among patients with Brugada syndrome irrespective of whether the Brugada ECG pattern is manifested or concealed.[10] Ikeda et al[11] studied LP among patients with Brugada syndrome and found that it can even be used as a noninvasive risk stratifier in these patients. To date, there is as yet no study to examine whether LP on SAECG is useful in family screening for the syndrome. In this study, we were able to demonstrate in this small cohort of subjects that LP in SAECG has a 100% sensitivity and negative predictive value in predicting the results of FPT. The

clinical implication of these results is that in conducting family screening for Brugada syndrome, we can start by recording both 12-lead ECG and SAECG. If the 12-lead ECG does not show any Brugada ECG pattern, FPT should be followed to look for any concealed form of the Brugada syndrome. But for those asymptomatic subjects who are reluctant to undergo FPT which requires venipuncture and intravenous drug infusion under close cardiac monitoring, a negative LP on their SAECG should reliably predict a negative FPT and FPT might be spared. However, if a positive LP is found, they should be strongly encouraged to undergo FPT.

This study has the following limitations. Firstly, the number of tested subjects in this study is small. Whether the results in this preliminary study apply to family screening in all patients with Brugada syndrome remains to be clarified in future study which should include a larger number of subjects. Secondly, the definitions of positive LP in SAECG and positive FPT vary among different studies. The results of this study are applicable only in situations where the current definitions used in this study are adopted.

Conclusions

LP on SAECG has a high sensitivity and negative predictive value in predicting the results of FPT used in family screening for Brugada syndrome. SAECG using a time domain analysis should be included as an additional non-invasive diagnostic tool in family screening for Brugada syndrome. Asymptomatic subjects with a negative LP could be reassured absence of the disease and FPT might be spared. However, subjects with a positive LP should undergo FPT to look for any concealed form of the syndrome.

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