行政院國家科學委員會專題研究計畫　成果報告

電腦模擬基因缺陷導致心室心律不整暨抗心律不整藥物治療

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中　華　民　國 94 年 10 月 28 日

行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

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　　謝士明
計畫參與人員：　林順國　楊雅筑

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中文摘要

1795insD及I1768V基因變異導致鈉離子通道功能改變而造成臨床上LQT症狀。然而， 臨床上對使用抗心律不整第三型藥物治療 LQT引發心律不整的機制並不清楚。 本研究以電腦模擬 795insD及I1768V基因變異引發LQT症狀 並透過阻斷 I_{K1}、I_{Kr}、I_{Ks}三種鉀離子通道模擬抗心律不整第三型藥物。實驗結果發現(1) 含I1768V變異基因之模擬細胞，於刺激間隔1000ms，及阻斷 90% I_{Kr}，在第五個動作電位會有早期後去極化產生;刺激間隔 1500ms，及阻斷 80% I_{Kr}，第三個動作電位有早期後去極化產生; (2)含I1768V變異基因之模擬細胞，於刺激間隔 500ms及阻斷 60% I_{Ks}之條件下，會有早期後去極化現象產生並惡化成心律不整; (3)藉著matlab 平行計算環境的使用， 動作電位在心室組織上的傳導可成功地轉換成心電訊號。本研究發現 1795insD及I1768V基因在阻斷I_{Ks}、I_{Kr}時，皆會產生早期後去極化現象，但是含I1768V變異基因的鈉離子通道在阻斷I_{Ks} 更容易引發早期後去極化現象，此現象是可能造成心律不整因素。

關鍵詞: 基因、離子通道、電腦模擬、平行計算

Abstract

1795insD and I1768V, two mutant genes, were recognized to have the ability to initiate long QT (LQT) syndrome. However, their arrhythmic vulnerabilities with the use of class III antiarrhythmic medications has not yet been explored. In this research,, the two mutant SCN5A ion channels were tested to elucidate the interactions among potassium channels, I_{K1}、I_{Kr} and I_{Ks} with by computer simulation. The results indicated (1) by blocking 90% I_{Kr} with current stimuli at the interval 1000ms, the action potential of I1768V at the 5^{th} beat began to display early depolarization; by blocking 80% I_{Kr} with current stimuli at the interval 1500ms, the action potential of I1768V at the 3^{th} beat began to display early depolarization ; (2) in vulnerable simulations, the stimulus interval was 1500 ms and Iks was 60% blockage, which resulted in early afterdepolarization and degenerated into arrhythmias on the incorporated I1768V cell model.; and (3)that action potential propagated on a cardiac sheet can be simulated and converted into to virtual E.C.G.. by parallel computing under matlab. Based on the results, both of 1795insD and I1768V could result in clinical LQT by the use of blockage of Ikr, and Iks. However, .the blockage of I_{Ks} for I1768V might cause serious early afterdepolarization than the blockage of I_{Kr}.

Keyword: gene, ion channel, computer simulation, parallel computing

前言

Long QT interval (LQT)是臨床心臟醫學上常見症狀，此疾病可能會快速地轉變成心律不整並導致心室顫動死亡。因此，治療 LQT 是臨床心臟醫學極欲解決的課題之一。目前，臨床上用藥治療 LQT 疾病，多半是使用第三類的抗心律不整藥物，其作用原理是部分阻斷鉀離子通道，藉以延長心臟動作再極化過程，以減少心律不整發生的可能性，但是整個抗心律不整的機制並不清楚。隨著，分子生物的快速發展，一些引起 LQT 疾病的基因陸續地被發現，例如 1795insD、I1768V。這些基因的變異，會改變鈉離子通道的物理特性，造成臨床上 LQT 的表現。然而，這些變異基因引起的 LQT，與第三類抗心律不整藥物的交互作用也並不清楚。如果能夠釐清第三類抗心律不整藥物與變異基因引起 LQT 的電生理特性，就能夠提供基礎醫學人員，開發新藥的可能方向，同時，提供臨床醫學人員對 LQT 的用藥策略。

研究目的

本研究的主要目的是利用數學模型建構出含有引發 LQT 之基因變異的鈉離子通道新式細胞模型，利用此一模型，探討阻斷特定鉀離子通道與 1795insD、I1768V 基因變異的鈉離子通道的交互作用，並模擬臨床第三類抗心律不整用藥策略。並根據模擬的結果找出最佳的用藥策略。本計劃除了探討基因變異引發 LQT 的電生理特性外，並希望能夠進一步擬出“虛擬”的簡易心電訊號 QRS，T 波以了解 LQT 的發生機制。

研究方法

本研究以Rudy於 1994 年提的心室細胞膜型作為藍本 [1]建構心臟心室細胞模型，早期Rudy以Hogkin-Huxly描述離子通道已不能適切地描述單一離子通道的特性，因此本研究部分修正部分Rudy 於 1994, 2001、2002 年發表的I_{Na}、I_{Kr},馬可夫鏈 (Markovian chain)離子通道動力模型並[2,3,4,5]並加入 1795insD、I1768V變異基因所引發的不正常鈉離子通道動力模型以模擬LQT 病症之電生理特性，數值計算部分我們使用解偏微分方程工具CVode (ordinary differential equation solver, ODE solver)計算細胞之電流電壓之變化 [6]，同時使用電壓箝制術(voltage clamp technique)的原理去固定細胞的電壓 [7]，藉此觀察離子通道的電流電壓的物理特性。

1. 鈉離子通道的數學模型建立

正常的 鈉離子通道可以以圖 1 表示 [4], 其中 C 表示通道處於關閉狀態,O 表示通道處於開啟狀態,I 表示通道處於抑制狀態。 此模型已廣泛地應用於模擬鈉離子通道電生理並證實可以適切地描述實驗結果[3, 4, 8, 9]。。

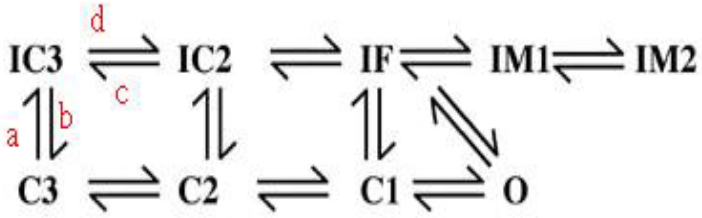

圖 1　鈉離子通道狀態示意圖[4] 。

2. 變異基因 1795insD、I1768V I_{Na}數學模型建立

1795insD 及 I1768V 可由前述的鈉離子通道模型修正後以十三個馬可夫鏈狀所組成，其微分方程如下[3,4]。

$$\frac{dUIC3}{dt} = -(a3+a11)\times UIC3 + b3\times UC3 + b11\times UIC2 \quad (1\text{-}1)$$

$$\frac{dUIC2}{dt} = -(b11+a3+a12)\times UIC2 + a11\times UIC3 + b3\times UC2 + b12\times UIF \quad (1\text{-}2)$$

$$\frac{dUIF}{dt} = -(b12+a3+b2+a4)\times UIF + a12\times UIC2 + b3\times UC1 + a2\times UO + b4\times UIM1 \quad (1\text{-}3)$$

$$\frac{dUIM1}{dt} = -(b4+a5)\times UIM1 + a4\times UIF + b5\times UIM2 \quad (1\text{-}4)$$

$$\frac{dUIM2}{dt} = -(b5)\times UIM2 + a5\times UIM1 \quad (1\text{-}5)$$

$$\frac{dUC3}{dt} = -(b3+a11+U2L)\times UC3 + a3\times UIC3 + b11\times UC2 + L2U\times LC3 \quad (1\text{-}6)$$

$$\frac{dUC2}{dt} = -(b11+b3+a12+U2L)\times UC2 + a11\times UC3 + a3\times UIC2 + b12\times UC1 + L2U\times LC2 \quad (1\text{-}7)$$

$$\frac{dUC1}{dt} = -(b12+b3+a13+U2L)\times UC1 + a12\times UC2 + a3\times UIF + b13\times UO + L2U\times LC1 \quad (1\text{-}8)$$

$$\frac{dUO}{dt} = -(b13+a2+U2L)\times UO + a13\times UC1 + b2\times UIF + L2U\times LO \quad (1\text{-}9)$$

$$\frac{dUC3}{dt} = -(L2U + a11) \times UC3 + U2L \times UC3 + b11 \times LC2 \quad (1\text{-}10)$$

$$\frac{dLC2}{dt} = -(b11 + L2U + a12) \times LC2 + a11 \times LC3 + U2L \times UC2 + b12 \times LC1 \quad (1\text{-}11)$$

$$\frac{dLC1}{dt} = -(b12 + L2U + a13) \times LC1 + a12 \times LC2 + U2L \times UC1 + b13 \times LO \quad (1\text{-}12)$$

$$\frac{dLO}{dt} = -(b13 + L2U) \times LO + a13 \times LC1 + U2L \times UO \quad (1\text{-}13)$$

(a*、b*、U2L、L2U 為速率常數)

I1768V 的馬可夫鏈動力模型與 1795insD 相同，但速率常數不一樣。

3. 電生理特性的模擬

利用細胞膜電壓箝制技術的原理 利用此模型 我們可以得到正常鈉離子通道 及基因變異的鈉離子通道的電生理之活化特性 非活化特性 及細胞興奮性測試 最後利用 我們先前使用的 s1-s2 刺激模式模擬基因變異的鈉離子通道與特定阻斷的鉀離子通道的交互作用。

4. 心電訊號模擬

最後我們將單一細胞模型擴展成二維的心室組織藉以模擬動作電位的傳導現象並估算肢導程的 QRS 及 T 波特徵。

結果及討論

圖 2A是正常、1795insD、I1768V三種不同鈉離子之活化過程特性曲線圖，結果顯示三條曲線並無太大差異，表示 1795insD、I1768V鈉離子通道從關閉開啟的Na^+離子動力與正常納離子通道相同。圖 2B是正常、1795insD、I1768V鈉離子通道非活化過程特性曲線圖，結果明顯看出 1795insD的曲線圖大概比正常左移 5±2mV，表示 1795insD變異基因會使得通道可用性降低，導致鈉離子通道從開-關過程中通過的Na^+電荷量減小;I1768V的曲線圖中大概比正常右移 17±2mV，表示 I1768V變異基因會提高通道可用性，使通道從開-關過程中通過的Na^+電荷量增加。正常、1795insD、I1768V鈉離子通道特性之恢復期分析結果

從圖 2C 中比較 WT、1795insD、I1768V 三種鈉離子通道的恢復期曲線，可明顯發現 1795insD 的曲線至少 500ms 後才趨近於正常，也就是說 1795insD 變異基因會使鈉離子通道的關閉過程趨緩減少可用性，綜合 1795insD 鈉離子通道可用性特性可推論出通道可用性特性與通道恢復期兩者的關係，1795insD 變異基因會

延長鈉離子通道非活化過程及降低使用率，導致鈉離子通道關閉時間延長。

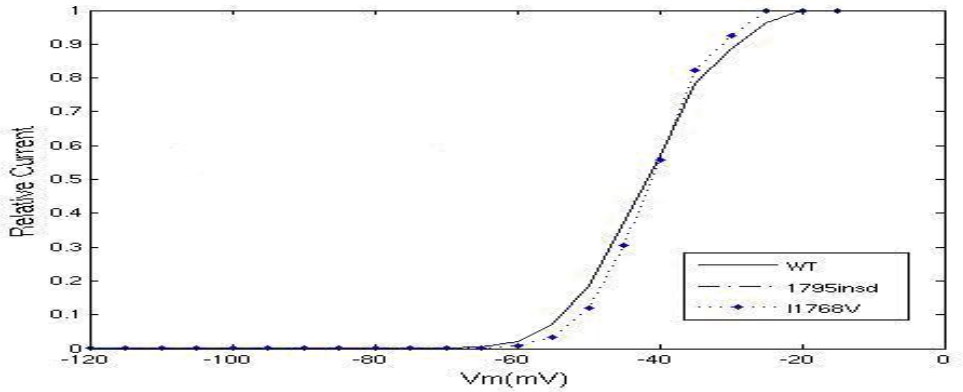

圖 2A 是正常、1795insD、I1768V 三種不同鈉離子之活化過程特性曲線圖。

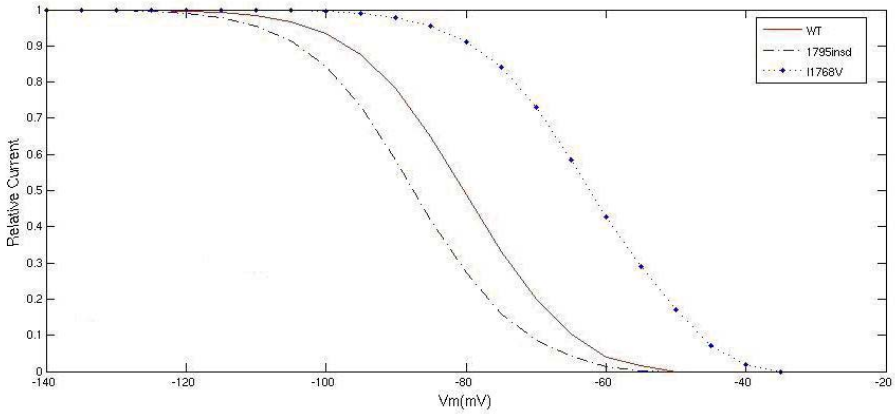

圖 2B 是正常、1795insD、I1768V 鈉離子通道非活化過程特性曲線圖。

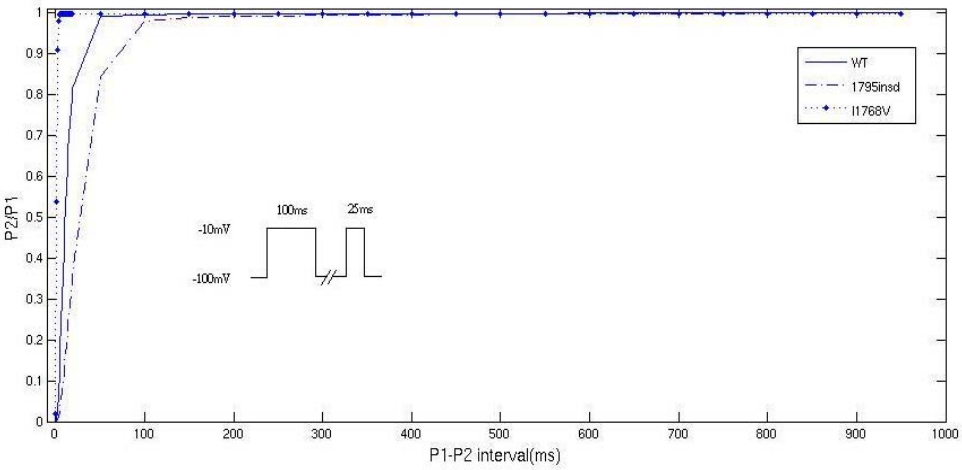

圖 2C 正常、1795insD、I1768V 三種鈉離子通道的恢復期曲線。

根據以上電生理特性模擬的結果，我們測試 1795insD和I1768V基因在阻斷I_{K1}、I_{kr}、I_{Ks}是否會引發過早去極化現象時發現，只有I1768V變異基因在阻斷Ikr離子

通道時才會有此現象產生，表 1 整理I1768V變異基因在不同的通道狀態時引發過早去極化現象的程度，圖 3A, 3B呈現測試結果。

表 1: I1768V 基因產生過早去極化現象統計表

	IK1		Ikr		IKs	
	阻斷比例	第 N 個 AP 產生 EADs	阻斷比例	第 N 個 AP 產生 EADs	阻斷比例	第 N 個 AP 產生 EADs
500ms	X	X	X	X	60%	9
1000ms	X	X	90%	5	50%	3
1500ms	X	X	80%	3	40%	6

* X 表示無發生過早去極化現象現象

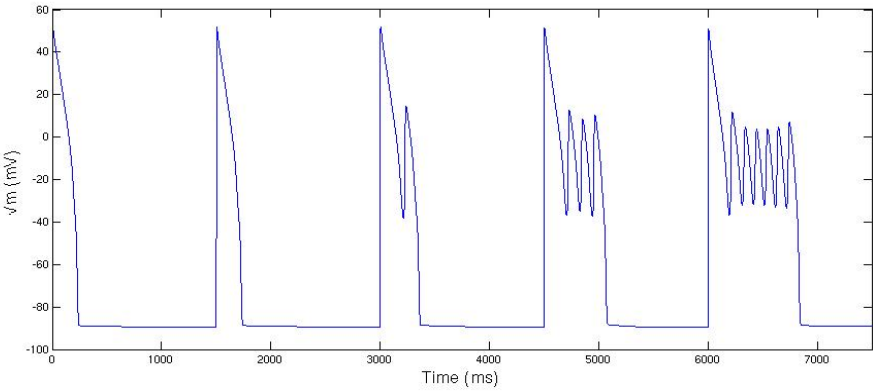

圖 3A I1768V基因過早去極化現象測試，阻斷I_{Kr}80%，刺激間隔 1500ms。

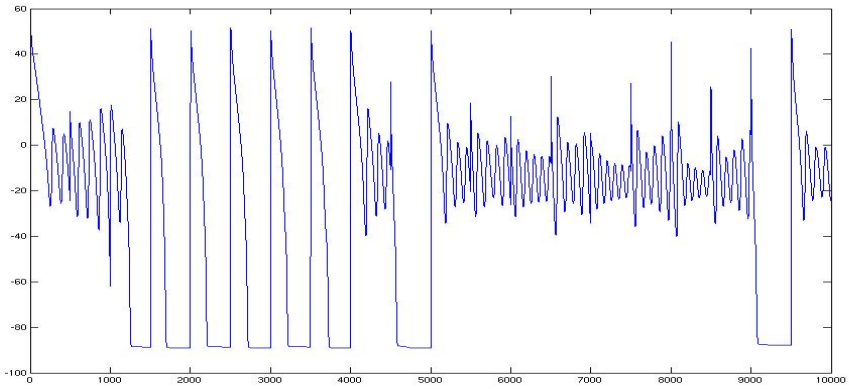

圖 3B 基因過早去極化現象測試，阻斷I_{Ks}60%，刺激間隔 500ms。

從阻斷離子通道的層面探討，阻斷I_{K1}時並不會有過早去極化現象的發生，且阻斷I_{Ks}比I_{kr}更容易使細胞發生過早去極化現象現象，而從刺激間隔層面來看，刺激間隔越大越容易產生過早去極化現象，此結果也解釋為何抗心律不整第三型藥物可能會引發Torsade de pointes 現象[10]。

圖 4 是心電圖 QRS 及 T 波之模擬。 我們將單一心室細胞擴展成一片心室組織以計算動作電位傳導時固定位置之電位差，再利用 matlab 分散式平行計算架構完成計算[11]。

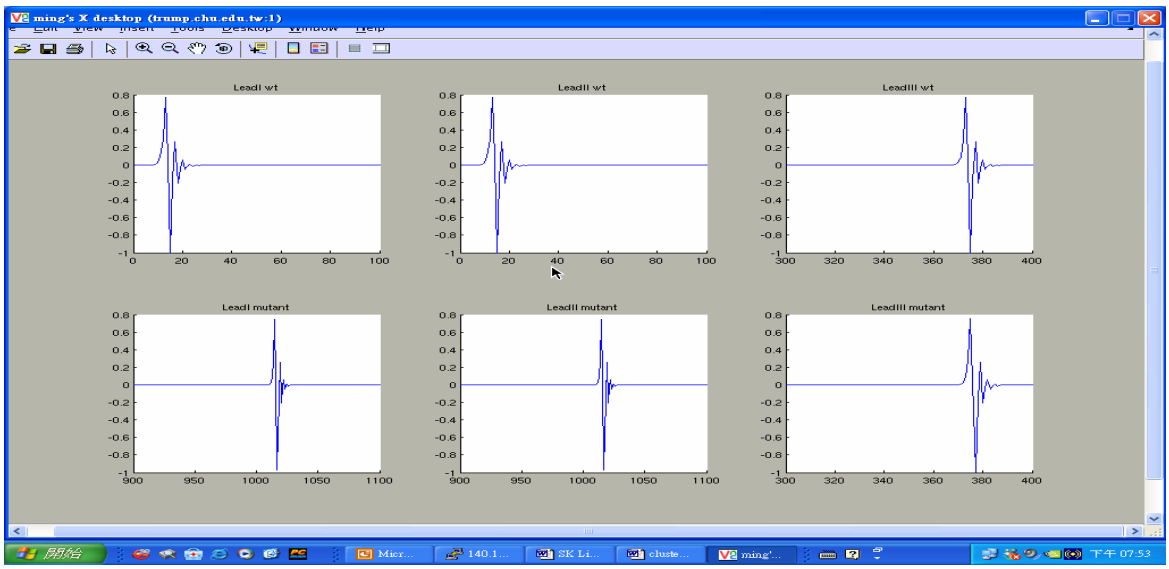

圖 4 心電圖 QRS 及 T 波之模擬。

計畫自評

本研究計畫於正常執行期限完成。主要完成有單一心室細胞模型，及 1795insD、I1768V 二種鈉離子通道基因變異數學模型，並成功模擬基因變異之電生理特性，及與特定鉀離子通道阻斷劑之交互作用。最後，利用個人電腦叢集之平行計算技術，完成虛擬心電訊號之 QRS、T 波。本研究計畫同時訓練資工所研究生林順國今年八月完成碩士論文。MATLAB 的平行計算技術已受邀於 matlab &simulink Technical forum and user conference 介紹 [11] 。根據模擬，我們得到一些有趣的結果，並可解釋臨床用藥上的一些盲點。本研究的部份結果已發表於 2005 年度 9 月 25 日～9 月 28 日於法國舉行的 Computes in Cardiology 國際會議[12]。未來可延續此模型，繼續發展基因變異對心電訊號特徵的影響。

文獻參考

1. Ching-hsing Luo and Yoram Rudy , "A Dynamic Model of the Cardiac Ventricular Action Potential - Simulations of Ionic Currents and Concentration Changes," Circulation Research *1994; 74: 1071-1097.*
2. Vivek Iyer, Reza Mazhari, and Raimond L. Winslow, "A Computational Model of the Human Left-Ventricular Epicardial Myocyte.", *Biophysical Journal September 2004;87:1507-1525.*
3. Colleen E. Clancy and Yoram Rudy, "Cellular consequences of HERG mutations in the Long QT Syndrome: Precursors to sudden cardiac death." *Cardivas Res 2001; 50: 301-313.*
4. Colleen E. Clancy, Yoram Rudy, "Na^+ Channel Mutation That Causes Both Brugada and Long-QT Syndrome Phenotypes : A Simulation Study of Mechanism." ,Circulation. 2002;105:1208-1213.
5. Vladimir E. Bondarenko,Gyula P. Szigeti,Glenna C. L. Bett,Song-Jung Kim,and Randall L. Rasmusson, "Computer model of action potential of mouse ventricular myocytes.", *Am J Physiol Heart Circ Physiol 2004;287: H1378–H1403.*
6. Alan C. Hindmarsh and Radu Serban, "User Documentation for cvode v2.2.1", *January 2005.*
7. Areles Molleman, "Patch Clamping: An Introductory Guide To Patch Clamp Electrophysiology," *Copyright 2003 John Wiley & Sons, Ltd.*
8. S Vecchietti, I Rivolta, S Severi, C Napolitano, SG Priori,S Cavalcanti, "Markovian Model for Wild-Type and Mutant (Y1795C and Y1795H) Human Cardiac Na+ Channel.", *Computers in Cardiology 2003;30:283-286.*
9. Colleen E. Clancy and Robert S. Kass, "Defective cardiac ion channels: from mutations to clinical syndromes", *J. Clin. Invest2002; 110:1075–1077.*
10. Lionel H.Opie, "Drugs for the Heart," 1995; 4th Edition.
11. Hsieh JC: Parallel Computing under Matlab. 2004 international Matlab & Simulink Tech Forum. (Invited Speaker)
12. Hsieh JC, Lin SK: Simulated Blocking of Potassium Channels Medication in Variant Gene-Mutant Sodium Channels. Computers in Cardiology 2005.(Accepted)

Simulated Blocking Potassium Channels Medication on Variant Mutant SCN5A Sodium Channels

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Abstract

Two gene-mutant sodium channels, 1795insD and I1768V, were considered to be the possible molecular markers in the initiation of long QT (LQT) syndrome. The 1795insD, which decreases the channel availability and enhances the inactivation, and I1768V, which increases the channel availability and enhances the rate of recovery from inactivation, have the ability to induce LQT regardless of their heterogeneous physical characteristics. However, their arrhythmic susceptibility with the use of certain antiarrhythmic medications has not yet been examined closely. In this study, the two mutant SCN5A channels were explored to elucidate the interactions among various potassium channels, IK1, IKr, and IKs with simulated antiarrhythmic medications by computer modeling. The two mutant SCN5A Markov models, adapted to fit into Rudy's ventricular cell model, performed numerical calculation by using cvode, an ODE solver, with C code in a 4-node PC cluster. In this study, our previously developed S1-S2 protocol was used to investigate the cell excitability in simulated blocking potassium channel medication. The results are as follows: (1) by blocking IK1 from 10% to 80%, the needed injection charges to initiate an action potential for 1795insD were smaller than I1768V's; (2) by blocking 70% IKr with current stimuli at the rate of 0.5Hz, the action potential of I1768V at the 4th beat began to display premature repolarization; and (3) by blocking 40% -50% IKs with current stimuli at the rates of 0.5 Hz and 1 Hz respectively, the action potential of I1768V at the 3rd beat and the 7th beat began to display premature repolarization. Accordingly, the blockage of IK1 could demonstrate both positive and negative effects on the two mutant SCN5A channels, as it may enhance or reduce the channel availability while increasing or decreasing the charge threshold. In addition, the blockage of IKs for I1768V might cause serious premature repolarization than the blockage of IKr.

1. Introduction

Recent studies have revealed that both mutant sodium channels, LQT 1795insD and I1768V, could result in clinical type III LQT syndromes [1, 2]. What is known about the physical properties of the 1795insD is that (1) it could decrease the channel availability and that (2) it could enhance the inactivation. Meanwhile, what is known about the physical properties of I1768V is that (1) it could increase the channel availability, and that (2) it could enhance the rate of recovery from inactivation [2]. The LQT in cellular level could display prolonged refractory. The class III antiarrhythmic drugs have been used as the major intervention on LQT. However, not much is known about the interactions between potassium channel blockers and mutant sodium channels. In this study, various potassium channel blockers, such as IK1, IKr, IKs, were simulated by reducing the maximum conductance of channels. The changes of action potentials were observed under various rates of stimuli from 0.5Hz to 1.5Hz and various potassium blockers. The vulnerability of mutant sodium channels were measured by the initiation of wave oscillation, which could prolong the action potential duration.

2. Methods

2.1. The model

Two gene-mutant sodium channels, 1795insD and I1768V based on Markov modeling, were incorporated into Rudy phase II cell model. The cell model was used to simulate the membrane excitability and ionic current activity under whole cell voltage clamp mode and current clamp mode. The relationships between membrane voltage and ionic currents are shown in Equation (1):

$$\frac{\partial V}{\partial t} = \frac{1}{C}(I_{ion} + I_{st}) \qquad (1)$$

Where V represents the membrane voltage, C represents the membrane capacitance, I_{ion} represents the summation of total ionic currents, and I_{sti} represents the

external current stimuli.

2.2. I-V relationship

To better understand the physical properties of the two mutant sodium channels, the current-voltage relationship simulation was performed on voltage clamp mode. In the same manner, the activation and inactivation curves of two mutant sodium channels were described by model simulation.

2.3. Cell excitability

To understand the interactions between potassium blockage and cell excitability under mutant sodium channels, the S1-S2 stimulus protocol was applied on the cell model to observe the possible changes of action potentials. Where S1 represents the conditional current stimulus to invoke action potential, S2 represents the test current stimulus.

2.4. The vulnerability of arrhythmias

To test the vulnerability of mutant sodium channel under various potassium blockers, the initiation of early after-depolarization was observed. In Figure 1, the initiation of early after-depolarization can prolong the action potential duration. Therefore, long QT interval can display on E.C.G [3].

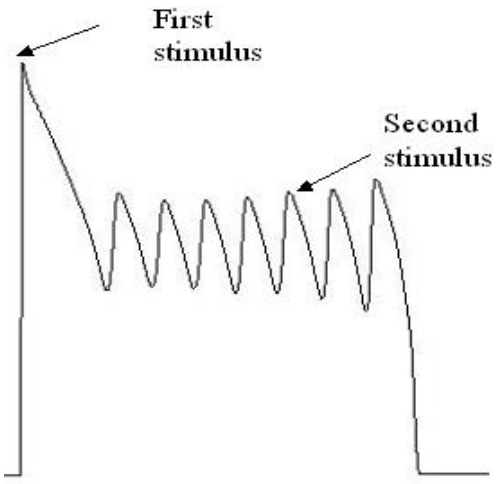


Figure 1. The initiation of early after-depolarization potential was used as the measurement of vulnerability.

2.5. Numerical computation

The system differential equations of ionic channels described by Rudy's phase II model and equation (1) were sent to a partial differential equation solver, CVode, running on a 4-node Linux cluster at the lab of system physiology and biology in Chung Hua University.

3. Results

3.1. Electrophysiological prosperities of sodium channel

To understand the electrophysiological characteristics of three sodium channels including wild type, 1795insD and I1768V, the current –membrane voltage (I-V) relationship were measured by their activation and inactivation process. In Figure 2A, the three sodium channels had similar I-V relationship during channel activation.

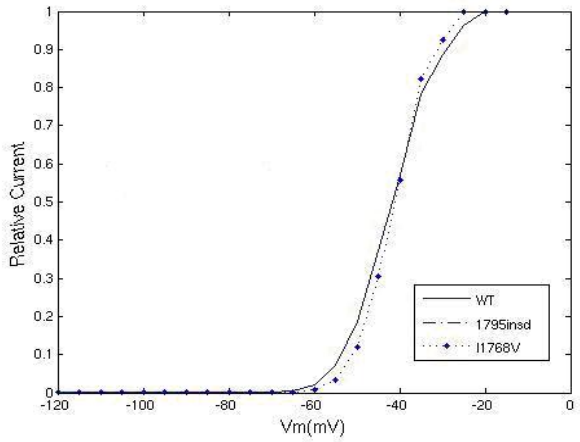


Figure 2A. Activation curves of three sodium channels including wild type, 1795insD and I1768V.

In the inactivation curve test, the three sodium channels showed large differences in electrophysiology. The inactivation cure of 1795insD was shifted to the left of wild type's; however, the inactivation curve of I1768V was shifted to the right. The result in Figure 2B indicated that the 1795insD enhances the inactivation process.

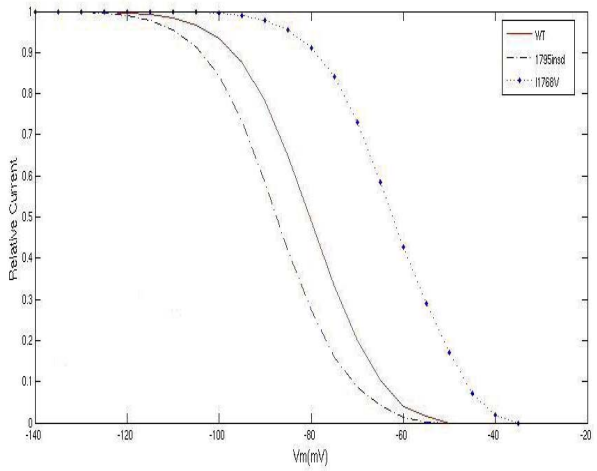


Figure 2B. The inactivation curves of three sodium channels: wild type, 1795insD, and I1768V.

As shown in Figure 3, the recovery rates from inactivation of three sodium channels were tested based on Rudy's protocol[], the I1768V on the left curve showed faster recovery rate than the wild type and 1795insD.

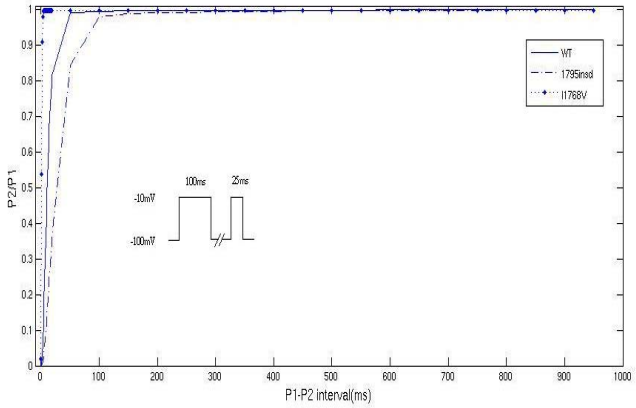
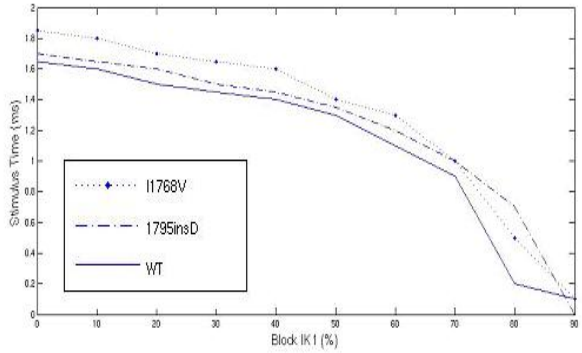


Figure 3. The curves of recovery rates from inactivation.

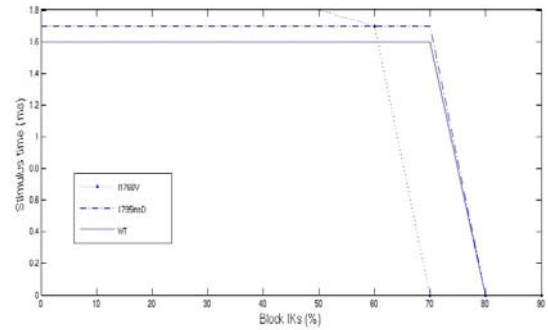
3.2. Cell excitability under potassium blockers

To better understand the interactions between cell excitability and potassium channel blockers, an S1-S2 current stimulus protocol was used to measure relative ratio of sodium currents by testing stimulus (S2) to the conditional stimulus (S1). In Figure 4A, the cell excitability was decreased with increased IK1 blockage in mutant and non-mutant sodium channels. However, I1798 showed higher excitability than 1795insD and the wild type sodium channel in IK1 blockage. As shown in Figure 4B, I1768V and 1795insD had the same degree of cell excitability despite of increased blockage of IKs from 40% to 70%. In Figure 4C, the cell excitability of three sodium channels remained the same despite of increased IKr blockage. However, the .I1768V had highest excitability among the three sodium channels under the same blockage of IKr.

(A)



(B)



(C)

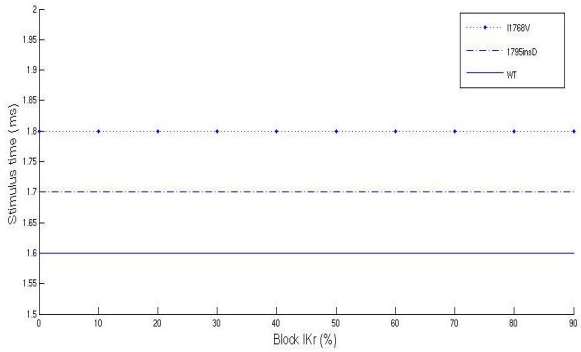
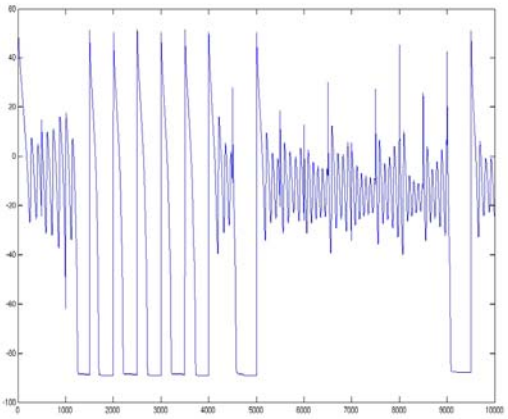


Figure 4 A,B,C. Cell excitability vs. various potassium channel blocker. The S1-S2 interval was 1500 ms.

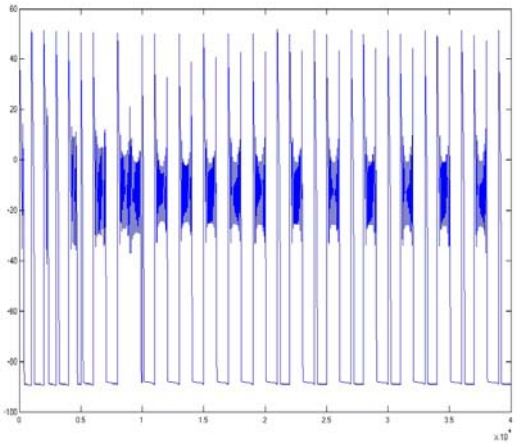
3.2. Vulnerability vs Potassium Blockers

The initiation of early afterdepolarization of action potentials was used as the vulnerability in this study. In Figure 5A, the stimulus interval was 1500 ms and Iks was 60% blockage, which resulted in early afterdepolarization and degenerated into arrhythmias on the incorporated I1768V cell model. In Figure 5B, the blockage of Iks was decreased to 50% and the stimulus interval was reduced to 1000 ms, and the early afterdepolarization was initiated. In Figure 5C, non-sustained early afterdepolarization was observed on the 80% of blockage of Ikr at 1500 ms stimulus interval.

(A)



(B)



(C)

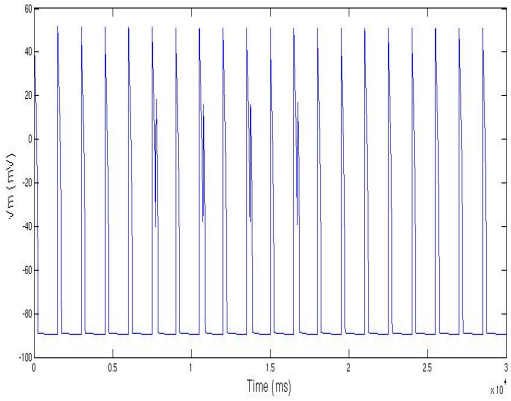


Figure 5 A,B,C. The initiation of early afterdepolarization of mutant I1768V cell model under various IKs channel blockage.

4. Discussion

Based on out simulations, the needed injection charges to initiate an action potential for 1795insD were smaller than I1768V's by blocking IK1 from 10% to 80%. Accordingly, the blockage of IK1 could demonstrate both positive and negative effects on the two mutant SCN5A channels, as it may enhance or reduce the channel availability shown in Figure 4 while increasing or decreasing the charge threshold. Based on the simulations shown in Figure 5, it was found that the blockage of IKs for I1768V might cause more serious premature afterdepolarization than the blockage of IKr.

Acknowledgements

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References

[1] Rivolta I et, al. A novel *SCN5A* mutation associated with long QT-3: altered inactivation kinetics and channel dysfunction. Physiol Genomics 2002;10: 191-197.

[2] Clancy CE, Rudy Y. Na^+ Channel Mutation that Causes Both Brugada and Long-QT Syndrome Phenotypes : A Simulation Study of Mechanism. Circulation 2002;105:1208-1213.

[3] Splawski I e,t al.: Variant of SCN5A Sodium Channel Implicated in Risk of Cardiac Arrhythmia. SCIENCE 2002; VOL 297:1333-1336.