

行政院國家科學委員會專題研究計畫 成果報告

繼發於後天性心臟右側枝傳導不良之QT延長是否會影響心臟之repolarization而導致心律不整：由臨床資料之分析到動物模式之確立(3/3)
研究成果報告(完整版)

計畫類別：個別型
計畫編號：NSC 95-2314-B-002-018-
執行期間：95年08月01日至96年07月31日
執行單位：國立臺灣大學醫學院小兒科

計畫主持人：吳美環
共同主持人：王主科
計畫參與人員：專科畢-專任助理：陳秋玉

報告附件：出席國際會議研究心得報告及發表論文

處理方式：本計畫可公開查詢

中華民國 96 年 10 月 31 日

行政院國家科學委員會補助專題研究計畫成果報告

繼發於後天性心臟右側枝傳導不良之 QT 延長是否會影響心臟之 repolarization 而導致心律不整：由臨床資料之分析到動物模式之確立

計畫類別： 個別型計畫 整合型計畫

計畫編號：NSC 95-2314-B-002-018

執行期間： 95 年 8 月 1 日至 96 年 7 月 31 日

計畫主持人：吳美環 台大醫學院小兒科

共同主持人：王主科 大醫學院小兒科

計畫參與人員： 吳恩婷 大醫院小兒科

成果報告類型(依經費核定清單規定繳交)： 精簡報告 完整報告

本成果報告包括以下應繳交之附件：

- 赴國外出差或研習心得報告一份
- 赴大陸地區出差或研習心得報告一份
- 出席國際學術會議心得報告及發表之論文各一份
- 國際合作研究計畫國外研究報告書一份

處理方式：除產學合作研究計畫、提升產業技術及人才培育研究計畫、列管計畫及下列情形者外，得立即公開查詢

涉及專利或其他智慧財產權， 一年 二年後可公開查詢

執行單位：臺大醫學院小兒科

中 華 民 國 96 年 10 月 31 日

一、中文摘要

背景 後天完全右側束傳導障礙常發生於開心手術後的法洛氏四重症病人。這些病兒因完全右側傳導障礙，也會有繼發性 QT 間距延長。而近日之研究顯示法洛氏四重症術後之病兒，仍有約 3%~10% 的機會出現心律不整，甚或造成猝死。在法洛氏四重症術後病人，心室性心律不整是重要的長期追蹤死亡原因。長期追蹤心律不整的危險因素包括容積負荷及電性不穩例如 QT 離散度增加。大部分法洛氏四重症術後心電圖會呈現完全性右側傳導支阻斷而造成後天性 QT 延長，因此本研究以臨床病例分析及動物實驗模式來探討後天完全右側傳導障礙的生理意義。我們假設因開刀造成的後天右側傳導支障礙會造成 QT 延長，進而增加心室性心律不整危險。

方法 1) 在臨床部分，我們前瞻性追蹤卅位法洛氏四重症及心室中隔缺損病人，觀察心電圖及心臟超音波變化臨床資料分析 2) 在動物實驗部分，我們以狗的模式模擬法洛氏四重症術後。第一組接受右側傳導支電燒及右心室剖開，第二組接受右心室出口人工膜重建。在開始及追蹤一年後我們會評估包括心電圖，植入性心電圖事件記錄器，及電生理檢查。另外我們也會評估藥物對於心室性心律不整的作用。

結果 1) 臨床資料分析: 前瞻性資料分析發現我們發現 QRS 及 QTc 間距在法洛氏四重症及心室中隔缺損術後都有增加，其中以法洛氏四重症較為明顯(QRS 121ms vs. 105ms, QTc 491ms vs. 454ms)。在兩年追蹤後，QRS 間距會更為延長，約每年 5.5ms，但此增加在心室中隔缺損並不明顯，QT 離散度也顯示在法洛氏四重症病人會隨時間延長。

2) 在動物實驗部分，肺動脈逆流在第二組接受右心室出口人工膜重建較為嚴重，而 QRS 延長則在右側傳導支電燒組較為嚴重。在心電圖指標，我們發現所有包括 QRS 間距，QTc 間距，JTc 間距及 QT 離散度在一年追蹤後都有增加，然而此增加除了 QT 離散度在外科組增加較多外，在兩組差異

並不明顯。在藥物測試中，我們發現 Inderal 可減少心室性心律不整的心電圖指標而有保護效果，但此效果會被 Procainamide 抵銷。而在事件記錄器資料分析我們發現在外科組追蹤超過半年後，心室性心律不整頻率在外科組明顯較多。而在電生理檢查中，在外科組有兩次誘發出心室性心律不整，而在電燒組則沒有。

結論 臨床病人分析顯示心電圖指標的變化在法洛氏四重症術後病人較心室中隔缺損術後病人來的明顯，且會隨時間而加重。在法洛氏四重症術後動物模式中，右側傳導支障礙及肺動脈逆流都是重要心室性心律不整因子，但其中又以肺動脈逆流影響較大。

關鍵詞：完全右側束傳導障礙、QT 間距延長、心律不整

ABSTRACT

Background: In surgically repaired tetralogy of Fallot (TOF) patients, ventricular arrhythmia is an important mechanism of late mortality. The risk factors of late arrhythmia include volume overload and electrical instability such as increased QT dispersion. Most of the repaired TOF patients would have complete right bundle branch block (RBBB) which may cause acquired QT prolongation. We proposed acquired RBBB by surgery may induce long QT which may cause vulnerability of ventricular arrhythmia in these patients.

Methods: 1) we prospectively invite 30 TOF and ventricular septal defect (VSD) patients to receive EKG and echocardiography follow-up, and the changes of EKG parameters will be evaluated.

2) Animal models of CRBBB by RF ablation and surgical RVOT patch were established in dogs. Group I received right bundle branch ablation and ventriculotomy, group II

received right ventricular outflow tract patch creation. EKG, extracardiac event loop recorder, and electrophysiology study by cardiac catheterization were evaluated before and after procedure and follow regularly up to one year. The drug response on ventricular arrhythmia were studied also.

Results In clinical study, we found also that QRS duration and QTc interval was significantly prolonged immediately postoperatively especially in TOF patients (QRS 121ms vs. 105ms, QTc 491ms vs. 454ms comparing TOF and VSD). During 2 years follow-up, QRS duration progressed further in TOF patients with QRS increasing 5.5ms per year but not in VSD patients. QT dispersion also increased during 2 year follow-up in TOF patients and not in VSD patients.

In animal part, pulmonary regurgitation was severer in those receiving RVOT patch, and QRS duration was longer in those receiving right bundle branch ablation. In EKG parameters, we found that all EKG parameters including QRS duration, QTc interval, JTc interval and QT dispersion all increased significantly during one year follow. However, these changes didn't differ significantly between surgical and ablation group except that QT dispersion increased more prominently in surgical group. In the drug effect study, we see that Inderal has protective effect in diminishing ventricular arrhythmia parameters in both groups after 1 year follow-up. The protective effect of Inderal is diminished by procainamide usage, although procainamide usage alone didn't have significant influence. In addition, by loop recorder recording, we can see more frequent ventricular arrhythmia including ventricular couplets, triplets, and short run ventricular tachycardia (VT) in surgical group after postoperatively more than half year. By electrophysiology study, 2 episodes of VT was ever induced in surgical group, but none was induced in ablation group.

Conclusions EKG parameters change is

more prominent in TOF than in VSD patients and may progress with time. RBBB and pulmonary regurgitation (PR) are both important in ventricular arrhythmia in repaired TOF animal model although PR played a more important role.

Keyword: complete right bundle branch block, QT prolongation, arrhythmias

二、緣由與目的

This three-year study aimed to define the physiological significance of complete right bundle branch block and its secondary QT prolongation. QT prolongation could be congenital or acquired. Congenital long QT syndrome is associated with mutations in Na or K channels. Patients with abnormally prolonged QT interval are prone to develop torsade de pointes ventricular tachycardia and sudden death. In the presence of bundle branch block, QT interval usually prolongs. However, the physiological significance has never been clarified. In repaired tetralogy of Fallot (TOF), the presence of complete right bundle branch block (RBBB) is common and the duration of QRS complex, if longer than 180 ms, had been shown to be a risk for sudden death during the long-term follow-up.

We had experienced two postoperative patients with TOF who developed life-threatening ventricular arrhythmias. Both had complete RBBB and progressively prolonged QT and JT intervals. Only after a temporary pacemaker with an adequate supporting heart rate and then an intracardiac defibrillator implantation, the condition was stabilized. From them and literature review, we hypothesized that 1) acquired complete RBBB can result in prolonged and possible inhomogeneous repolarization, that may also predispose the patients to have torsade de pointes ventricular arrhythmias; and 2) the proarrhythmic potential of such secondary QT prolongation may increase with time and may be potentiated by right ventricular volume overload.

In the first year, a pig-animal model to create the complete right bundle branch block had been established. However, because of the limited reference for basic physiological data in pigs, we then shifted to dogs in the latter part of the first year. We continued to use dog as the animal model this year.

In the second year, we have reviewed the preoperative EKG in patients with TOF identified from the database from 1976 to

2000 to define the possibility of combined congenital long QT syndrome and TOF patients.

In the third year, we have prospectively examined the development and consequences of CRBBB in repaired TOF and VSD patients. In the animal part, we have successfully established the dog model with surgical pulmonary regurgitation and created CRBBB. This animal model will provide the mechanisms for secondary effects of QRS and QT prolongation.

三、結果與討論

Part A: Prospective study on repaired TOF and VSD:

There was 21 tetralogy of Fallot (TOF) and 17 ventricular septal defect (VSD) patients received our follow-up. Preoperatively, there was no difference in EKG parameters including QRS duration, QTc duration, and QT dispersion in TOF group and VSD group. Early postoperatively, we can find complete and incomplete RBBB pattern and QRS duration prolongation in both groups (121 vs. 105ms in TOF and VSD groups). The magnitude of QRS duration prolongation is significantly larger in TOF groups. The same finding was also found in QTc duration. In TOF group, QTc duration increased to 491ms in TOF groups, but only mild prolongation to 454 ms in VSD group. However, for QT dispersion, the difference between TOF and VSD is not significant.

At mean 23 months follow-up, QRS duration prolongation persisted in both groups, with QRS 132 ms in TOF and 106ms in VSD groups, which was statistically different. The rate of QRS duration increase is 5.5ms per year in TOF group, and 1.4ms per year in VSD group. When comparing with early postoperatively, QRS duration

significantly prolong after 23 months follow-up in TOF patients ($p=0.006$), but not in VSD patients ($p=0.116$). For QTc interval, it also showed persistent prolonged QTc interval in both groups (486ms in TOF and 462ms in VSD groups). However, unlike QRS duration, QTc prolongation didn't progress further, and it even shorten slightly in TOF patients (but no statistically significantly). This result may be related to relative high heart rate at early postoperatively which cause QTc higher. If we compare QT interval (without Bazett correction) at early and late postoperatively, we can see still progressive QT interval prolongation at TOF group (QT interval 360ms at early and 388ms at late postoperative period). For QT dispersion, we can find QT dispersion increase from 20.8ms to 32.8ms after 2 years follow-up in TOF group, but this was not found in VSD group.

Briefly summary, in this prospectively clinical study, we can see immediate increase of QRS duration and QTc interval early postoperatively especially in TOF patients. QRS duration increases further during 2 years follow-up. Besides, QT dispersion increases during follow-up which may imply the increase ventricular arrhythmia risk after longer follow.

Part B: Animal model for repaired TOF

We performed angiography to define pulmonary regurgitation (PR) severity at week 52. We can find 5 severe PR and 2 mild PR in surgical group, but no significant PR in ablation group. Hemodynamic data at the end of study didn't show elevated RA pressure in both groups.

We performed EPS study at the baseline, 24th week, and 52th week. No ventricular

tachycardia (VT) was ever induced at baseline both in surgical group and in ablation right bundle branch block (RBBB) group. At 24th week, 1 episode of Vf has been induced in surgical group (1/7).

However, no VT has been induced in ablation group. At 52th week, no VT was induced in ablation group, but 1 episode of short run VT was ever induced in surgical group (1/4). However, it didn't show statistical significance because of relative small sample size and relative short follow-up period.

We also implanted loop recorder to record ventricular arrhythmia episode in both groups. In the first half year, there were average 1.5 ventricular couplet, 1.5 ventricular triplet, and 1 short run VT per month in surgical group. In ablation group, there were average 0.5 ventricular triplet and 1 short run VT per month in the first half year. No significant difference in both groups. However, in the last half year, there were average 25 ventricular couplets, 3 ventricular triplets, 5 short run VT, and 1 sustain VT per month in surgical group. It is statistical different from ablation group, which showed 1 ventricular triplet and 2 short run VT per month. So in loop recorder data, we see more frequent ventricular arrhythmia in surgical group after postoperatively greater than half year.

In EKG parameters, we found significant prolongation of QRS duration after procedure in ablation group which related to RBBB effect. At week 52, QTc duration was longer in ablation group, but after correction for QRS duration prolongation, we can see JTc duration was longer in surgical group. However, QT

dispersion showed no significant difference between both groups. When we analyze the serial EKG parameters change after the procedure, we noticed that QRS duration, QTc duration, JTc duration, and QT dispersion all progressively increased comparing week 2 and week 52 data (p value all <0.05). However, no significant difference in EKG parameters change was seen between these two groups except QT dispersion prolongation is larger in surgical group. So from EKG parameters change, we deduced that the ventricular arrhythmia parameters increased with time in both ablation and surgical groups. However, the parameters change didn't show significant differences between both groups except QT dispersion have a trend of progressively increase surgical group.

To see the drug effect on EKG parameters change, we used Inderal and Procainamide as test drugs. Before the procedure, no significant EKG parameters change was found under either Inderal or Procainamide. After the procedure at week 48, we saw protective effect of Inderal intake. QT dispersion decreased significantly under Inderal both in surgical or ablation groups, and there was also a trend of decrease QTc and JTc under Inderal use. No significant EKG parameters change under Procainamide intake at week 48 although there was a trend of increase JTc. If both Inderal and procainamide were used, there was only a trend of decrease QT dispersion and no change in QTc and JTC. Thus from drug effects data, we could find protective effect of Inderal use after the procedure both in ablation and surgical groups. However, this protective effect was diminished by

procainamide use.

五、參考文獻

Antzelevitch C, Shimizu M, Yan GX, et al. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol.* 1999; 10: 1124–1152

Berger R, Akselrod S, Gordon D, et al: An efficient algorithm for spectral analysis of heart rate variability. *IEEE Trans Biomed Eng.* 1986;33:900–904

Chandar JS, Wolff GS, Garson A, et al. Ventricular arrhythmias in postoperative tetralogy of Fallot. *Am J Cardiol* 1990;65:655-661.

Deanfield JE, McKenna WJ, Presbireto P, et al. Ventricular arrhythmia in unrepaired and repaired tetralogy of Fallot. Relation to age, timing of repair, and haemodynamic status. *Br Heart J* 1984;52:77-81.

Garson A, Nihill MR, McNamara DG, et al. Status of the adult and adolescent after repair of tetralogy of Fallot. *Circulation* 1979;59:1232-1240.

Garson A, Randall DG, Gillette PC, et al. Prevention of sudden death after repair of tetralogy of Fallot: treatment of ventricular arrhythmias. *J Am Coll Cardiol* 1985;6:221-227.

Gatzoulis MA, Till JA, Somerville J, et al. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation* 1995;92:231-237.

Gatzoulis MA, Till JA, Redington AN. Depolarization-repolarization inhomogeneity after repair of tetralogy of fallot: the substrate for malignant ventricular tachycardia? *Circulation* 95(2):401-404, 1997.

- Gelband H, Waldo AL, Kaiser GA, Bowman FO, Malm JR, Hoffman BF. Etiology of right bundle branch block in patients undergoing total correction of tetralogy of Fallot. *Circulation* 1977;44:1022.
- Gillete PC, Yeoman MD, Mullins CE, et al. Sudden death after repair tetralogy of Fallot: electrocardiographic and electrophysiologic abnormalities. *Circulation* 1977;56:566-571.
- Horowitz LN, Alexander JA, Edmunds LH Jr. Postoperative right bundle branch block: identification of three levels of block. *Circulation* 1980;62:319.
- Horowitz LN, Simson MB, Spear JF, Josephson ME, Moore EN, Alexander JA, Kastor JA, Edmunds LH Jr. The mechanism of apparent right bundle branch block after transatrial repair of tetralogy of Fallot. *Circulation* 1979;59:1241.
- Jonasson H, Ivert T, Brodin M, Jonasson R. Late sudden deaths after repair of tetralogy of Fallot. Electrocardiographic findings associated with survival. *Scand J Thorac Cardiovasc Surg.* 29(3):131-9, 1995.
- Klitzner T. Hereditary long QT syndrome in the postoperative cardiac patient. *Clinical Cardiology.* 13(2):139-42, 1990.
- Kobayashi J, Hirose H, Nakano S, et al. Ambulatory electrocardiographic study of the frequency and cause of ventricular arrhythmia after correction of tetralogy of Fallot. *Am J Cardiol* 1984;54:1310-1313.
- Krongrad E, Hetler SE, Bowman FO, Malm JR, Hoffman BF. Further observations of the etiology of the right bundle branch block pattern following right ventriculotomy. *Circulation* 1974;50:1105.
- Marie P, Marcon F, Brunotte F, et al. Right ventricular overload and induced sustained ventricular tachycardia in operatively "repaired" tetralogy of Fallot. *Am J Cardiol* 1992;69:785-789.
- Morady F, Higgins J, Peters RW, Schwartz AB, Shen EN, Bhandari A, Scheinman MM, Sauve MJ. Electrophysiologic testing in bundle branch block and unexplained syncope. *Am J Cardiol* 1984;54:587-591.
- Murphy JG, Gersh BJ, Mair DD, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med* 1993;329:593-599.
- Pomeranz B, Macaulay R, Caudill M, et al: Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol.* 1985;248:H151-H153
- Rosenthal A. Adults with tetralogy of Fallot—repaired, yes; cured, no. *N Engl J Med* 1993;329:655-656.
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation.* 1996;93: 1043-1065
- van den Berg MP, Wilde AA, Viersma TJW, et al. Bradycardic mode of death and successful pacemaker treatment in a large family with features of long QT syndrome type 3 and Brugada syndrome. *J Cardiovasc Electrophysiol* 12(6):630-6, 2001
- Yasui H, Yoshitoshi M, Komori M, et al. Hemodynamic effects of experimental right bundle branch block in canine hearts with normal and hypertrophied right ventricles. *Am Heart J* 109(1):69-77, 1985
- Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation.* 1998; 98: 1928-1936.

出席國際學術會議心得報告

計畫編號	NSC95-2314-B002-018
計畫名稱	繼發於後天性心臟右側枝傳導不良之 QT 延長是否會影響心臟之 repolarization 而導致心律不整：由臨床資料之分析到動物模式之確立(3/3)
出國人員姓名 服務機關及職稱	吳美環 台大醫學院小兒科
會議時間地點	2007/7/28-2007/7/31 拿大溫哥華
會議名稱	國際心臟學會大會
發表論文題目	

一、參加會議經過

此次參加第 13 屆世界心臟大會，主辦單位是 International Academy of Cardiology，也是這學會每年舉辦一次的年會。其學術會議共有 3 整天。由早上 8 點半到晚上 7 點半。每個時段中間只休息 15 分到 30 分鐘。可能是會議地點加拿大溫哥華，在比較北方，目前到晚上 9 點才會天黑，因為大家都覺得白天的工時較長，會議就由原來的 4 天集中成 3 天，這樣似乎效果也不錯。開完會，走出會議就如下午般，又是一個飽滿的晚上可以看看都市。夏天開會，似乎忙碌與悠閒是可以並存的。

此次開會除了另闢會場提供各國學者發表其最新的研究報告外，有相當多的 Plenary symposium 針對各項主題邀請世界的專家學者深入且系統性地為大家解說，讓與會醫師對於其專題能在 2 至 3 小時後，得到最即時的資訊。此次 Plenary symposium 的建構，多由基礎到臨床，學者相當多是 PhD。此次因小兒心臟科的主題與研究論文發表較少，而有較多的時間可以參與許多基礎研究主題的研討會，之後以不同的觀點再切入平常看似習慣的小兒心臟領域，倒也有相當不少的感想。僅摘錄一些心得如下：

二、與會心得

(一) Predictors and Markers of heart failure outcome

各項 Biomarker 的測量，由於是一種可以量化的指標，往往是學者們熱衷研究的主題。再加上近年 Genomics，Proteomics 等研究方法的推波助瀾，有關 heart failure 之各項 biomarkers 的測量就涵蓋了 matrix metalloproteinase (MMP)，extracellular collagen matrix (ECCM) heart shock protein 60 (HSP60)，natriuretic peptide (BNP) 等。

在成人 Heart failure 的主要原因是 myocardial ischemia，myocardial ischemia 之後 LV remodeling，繼而惡化其心衰竭或改變其心衰竭表現。以 collagen 而言，ECCM 是維持心臟型態與功能相當重要的一環，心肌缺氧變化後，MMP 以及 tissue inhibitor of MMP (TIMP) 之間的平衡是控制 ECCM 是否能產生適當的 collagen 的主因。有研究指出，當某種 MMP/TIMP profile 出現時可以預估此心肌梗塞病人可能合併 adverse LV remodeling 而易發生心衰竭。其中一個研究顯示，心肌梗塞第一天病人 MMP 就較控制組高了 150%，Cardiac specific TIMP-4 則在第 5 天下降，這些變化可維持多天，且與第 28 天左心室的擴大有密切正相關 (End diastolic volume 可增加 3 倍)。此外，TIMP-4 在心衰竭的病人也相對比控制組高。

因此各種藥物治療若能影響 MMP/TIMP 系統及 ECCM 的不適當反應，極可能改變其 LV remodeling。例如若 collagen 太少，較易導致 LV dilatation 及收縮功能不良而衰竭。反之，若產生過度 collagen，甚至 excessive cross-linked collagen，則可能導致 ventricular stiffness 增加，舒張功能不良而衰竭。目前已有研究的藥物，例如影響 Renin angiotensin system 的 ACE inhibitors 及 ARB 等，HMG-CoA reductase inhibitor (statins) 等皆可能影響 ECCM 系統而改變其 LV remodeling。但仍有相當多的交互關係待未來研究釐清。

此外，在心衰竭病人，HSP60 也極有可能與心肌細胞的 apoptosis 有關。HSP60 是種存在於 mitochondrial 及 cytoplasmic protein。特別的是，心肌受傷後，其 HSP60 會由

cytoplasm 移到 plasma membrane。進一步在心衰竭的老鼠模式更找到這些移到 plasma membrane rafts 的 HSP60 行為與 TNF 相似與 apoptosis 有關。

由這些研究大致可以將各種 biomarker 變化連接到臨床疾病階段。雖然應小心由動物實驗 explore 到疾病狀態的各種 limitations。但若能及早在疾病惡化早期以藥物等治療反轉其病程，也是重要的醫療切入點。

(二) Endothelial Dysfunction-Arterial Stiffness-Artherosclerosis

成人冠狀動脈疾病的相關研究極多，目前在 Endothelial dysfunction 這領域有相當多的研究成果。基礎研究在 vascular oxidative stress, redox signaling, inflammation, angiogenesis, bone marrow-derived endothelial progenitor cell 等皆有相當多的證據。在臨床方面，也有一些方法，有些初步的資料指出臨床評估 endothelium 功能的可能性。例如以 flow-mediated dilation 來偵測 endothelial dysfunction 以 Pulse wave velocity 等 index 測定 arterial stiffness 等。對於 preventive cardiology 醫療策略應有其用途。這些在兒童心臟學逐漸與 preventive cardiology 接軌之時，相關的研究在兒童心臟學將會是重要且熱門的課題。於此次大會筆者也將臺大醫院小兒心臟團隊治療兩側右心房症的成果介紹給大家。我國比起其他國家有較多的右心房同位症，治療的成果及繼而建立的醫療策略，是兩側右心房症醫療重要的參考資料。