附件：封面格式

行政院國家科學委員會補助專題研究計畫成果報告

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※ 非手術心室中隔厚度減少技術對正常豬隻及肥厚性心肌病變豬隻 ※
※ 左心室厚度減少，血行力學變化及傳導系統病變之動物模式研究 ※
※ Effect of nonsurgical septal reduction technique on the thickness of left ※
※ ventricle, hemodynamic and conduction system changes in normal swine ※
※ and swine with naturally occurring hypertrophic cardiomyopathy ※
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計畫類別：■個別型計畫　　□整合型計畫

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執行期間：88 年　8 月　1 日至　89 年　7 月　31 日

計畫主持人：黃水坤教授

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一、中文摘要

肥厚性心肌病變為一先天性心臟肌肉病變，罹患此症之病患多會併發心臟衰竭，心絞痛或心臟猝死。左心室出口部阻塞被視為重要的血行力學變化，而改善左心室出口部阻塞在臨床上為治療的考慮要點之一。此病的治療方法有藥物治療，外科手術治療及雙腔室心律調節器置放等方法。

1995 年，Sigwart 氏發表經由心導管的方法選擇冠狀動脈左前降枝的心室中隔分枝注射絕對酒精，造成局部心肌梗塞，進而減少心室中隔厚度，改善左心室出口部的阻塞,初步觀察，臨床上有顯著療效。

但此一方法容易導致心律不整的發生，最常見為右束枝傳導阻滯，約 52 至 85%，其次為完全性房室傳導阻滯，約 60 至 65%，其中 20%需置放永久性心律調節器。

本研究目的有二。首先為建立豬隻模式之心導管技術，尤其是約 2mm 之心室中隔分枝等技術困難之小血管。其次為觀察酒精注射後心電圖變化，心臟超音波指數及傳導系統之影響程度等。

本研究前三隻豬隻均在實驗隔天或當天死亡。病理檢查可見左前降枝均有大量血栓，經酒精注射(約 5 至 十秒) 之第二，三隻豬隻另可見房室結嚴重纖維化。此結果提示肝素等抗凝血劑在此手術非常重要，剛開始實驗之技術及豬隻冠狀動脈立體結構之不熟悉使操作時間太長亦有關連(約一小時)。此外，太快注射酒精也易導致急性併發症，如第三隻豬隻，注射完後立即產生致命性心室纖維顫動。

改進此上幾點，即無突然猝死之實驗豬隻。共有 4 隻豬隻成功接受心室中隔分枝絕對酒精注射。其中只有一隻心電圖出現右束枝傳導阻滯，並無完全性房室傳導阻滯發生。有一隻心電圖出現較明顯之 V1 至 V4 導程 ST-T 節段上升。度量 QT dispersion 可見 QTd 在酒精注射後明顯上升，而在 1 至 2 週後恢復為 baseline。(注射前：50±8.2 msec，注射後：77.5±9.6 msec, P<0.01；1 至 2 週後：47.5±9.6 msec 與注射後比較, P<0.01)。心臟超音波檢查顯示心室中隔厚度在酒精注射後減少(11.75±0.96 mm vs9.25±0.96 mm, P<0.01)。病理檢查顯示心室中隔有局部性心肌梗塞，左前降枝冠狀動脈內並無血栓，而傳導系統大致完好。

本研究提供實驗豬隻心導管技術的建立。抗凝血劑的使用及緩慢注射酒精均為臨床上治療病患之重要事項。豬隻較少有傳導阻滯之發生可能與側枝循環有關。本研究發現酒精注射後 QT dispersion 明顯延長，與此注射造成之局部心肌梗塞相關，心律不整的預防在此些病患尤需注意。

二、緣由與目的

Background

Hypertrophic cardiomyopathy is one of the congenital disease of the myocardium. The World Health Organization defines it as an idiopathic heart muscle disorder characterized by unexplained left ventricular hypertrophy. Many patients have mild disease which may go unnoticed or may be accidentally detected. Symptoms,when they occur, are in the form

of chest pain, dyspnea, syncope and palpitations and are due to ischemia, high left atrial pressure and repetitive arrhythmias. Most of the symptoms are caused by obstruction of the left ventricular outflow tract, and relief of this obstruction is usually followed by clinical and hemodynamic improvement. Choices of treatment in hypertrophic cardiomyopathy include drug therapy (Beta-blocker, nondihydropyridine calcium channel antagonist), surgery (ventricular septal myotomy-myectomy, mitral valve replacement) and the controversial dual-chamber pacing.

Sigwart described a novel technique of non-surgical reduction of the septal bulge in patients with advanced hypertrophic obstructive cardiomyopathy in 1995. He injected absolute alcohol through an inflated balloon catheter into the first and/or second septal perforators to produce a localized infarct. Hemodynamic improvement, especially in reducing the pressure gradient across the left ventricular outflow tract, was observed at both short-term and mid-term follow-up after non-surgical septal reduction therapy.

However, development of arrhythmias occurs not infrequently after the procedure. On the basis of clinical experience, the commonest arrhythmia reported in association with septal alcohol injection is right bundle-branch block, which occurs in 52 to 85 % of patients so treated. Complete heart block has been reported to occur in 60 to 65 % of patients, with about 20 % of those requiring permanent pacemaker implantation.

The purpose of this study is two-fold. Firstly, with the collaboration of Pig Research Institute, Taiwan, we will set up the cardiac catheterization technique in pig model, especillay in the alcohol ablation of the septal perforators of about 2mm in diameter. Secondly, the effect of septal alcohol ablation on the heart will be evaluated by electrocardiogram, echocardiogram, and pathological examinations with the emphasis on the thickness of interventricular septum and changes in the conduction system.

Materials and Methods

Six-month-old pigs weighing about 80 to 100 kg are eligible for this study. All animals received anesthesia with 12 mg/kg ketamine intramuscularly and 10 mg/kg thiamylal intravenously. Vascular access will be via carotid or femoral vessels by Seldinger's technique or direct cutdown. Aortic and left ventricular pressures were measured. Heparin 10,000 units were given intraarterially. Left coronary artery was cannulated using the 7F Judkins left or Multipurpose guiding catheter. The X-ray C-arm was adjusted obliquely and caudal-cranially to get the best view for selecting the left anterior descending and first septal perforator. After this, over-the-wire balloon catheter with the diameter 2.0 or 2.5 mm was introduced into the target vessel under the direction of guidewire deeply situated at the vessel. Two to three miniliters of absolute alcohol were injected through the over-the-wire balloon slowly into the target vessel after balloon was inflated. The animal was observed for 10 minutes and then sent back for follow-up studies.

Twelve-lead electrocardiography was performed before, immediately after septal alcohol injection and one to 2 week follow-up examinations. Echocardiogram was obtained before and one to 2 weeks later. Then the

animals were sacrificed and the heart was procured for pathological studies.

Results and Discussion

1) Feasibility of septal perforator selection in pig model

1. Vascular access

We tried to puncture the femoral vessels via Seldinger's technique, but it was difficult to introduce the sheath into the vessels even under C-arm guidance due to tortuous vessels in this region. Then, we shifted to direct cutdown of carotid artery in the following experiments.

2. Selection of left coronary artery and first septal perforator

We could easily cannulate the left coronary artery using the 7F Judkins left or Multipurpose guiding catheter through the right or left carotid artery. Left and right coronary arteries could be clearly visualized after contrast injection, but the branches were obscure under the C-arm at Pig Research Institute. The first pig died suddenly next day following the experiment and necropsy was done. The second experiment was undertaken at the Animal Laboratory of College of Medicine, National Taiwan University. The septal perforator could be identified and balloon catheter was inserted into it through guidewire after about 60 minutes of manipulation. Two ml of absolute alcohol was injected over 10 seconds and the pig also died next day. At the third experiment we also successfully infused 2 ml of alcohol rapidly into the septal perforator, but the pig developed ventricular fibrillation with extensive anterior wall infarction documented by electrocardiogram. Multiple DC shock were given, but in vain. All of the three animals demonstrated thrombus at the left coronary system at necropsy. The infarct area extended from the interventricular septum to the anterior wall of left ventricle with fibrosis involving the AV node. It suggests that the heparin dosage was not enough and longer manipulation under poor C-arm guidance and learning curve in the identification of coronary trees in pig is a major limitation of this study. Too rapid injection of alcohol might also contribute to the acute complication. Afterwards, we increased the heparin to 15,000 units and slow injection of alcohol over 1 to 2 minutes was used. No unexpected death occurred thereafter.

2) Electrocardiographic changes after successful septal alcohol ablation

A total of 4 pigs successfully undertook septal alcohol ablation with average of 2.5 ml of alcohol. One pig developed right bundle-branch block and another one had ST-T elevations over leads V1 to V4. No complete AV block occurred. We measured the QT max, QT min and calculated the QT dispersion in these animals.

QT dispersion was increased after alcohol injection and returned to baseline 1 or 2 weeks later (before: 50 +/- 8.2, immediately after: 77.5 +/- 9.6, $P<0.01$; late: 47.5 +/- 9.6, $P<0.01$ vs immediately after). The main change was decrease in the QT min (before:377.5 +/- 27.5, immediately after: 350 +/- 18.3, $P=0.07$;

late: 372.5 +/- 22.2, P=0.08 vs immediately after).

3) Echocardiographic measurements

The thickness of interventricular septum decreased from 11.75 +/- 0.96 to 9.25 +/- 0.96 (P<0.01). The left ventricular ejection fraction (72.5 +/- 4.1 vs 72.8 +/- 1.5), the thickness of left ventricular posterior wall (11.0 +/- 0.82 vs 11.25 +/- 0.5) and the left atrial diameter (31.75 +/- 2.63 vs 31.25 +/- 1.71) were not changed significantly 1 or 2 weeks after alcohol injection.

4) Pathological findings

All of the 4 animals demonstrated infarct area at the interventricular septum. No intracoronary thrombus was found. The involvement of conduction system was not apparent.

Self-evaluation of this study

Set-up of cardiac catheterization technique in the pig model even in the small vessels was achieved from this study. Adequate heparinization and slow injection of alcohol during the procedure gave important implication for this modality in treating patients. The rare occurrence of conduction disturbance in pigs may be species difference in the collaterals of conduction system. Interestingly, we found significant QT dispersion immediately after septal alcohol ablation, although we cannot be sure its relation to proarrhythmic effect of this procedure. We still need to take care of localized infarction in patients receiving it.

References

1. McKenna W, Dearfield J, Feruqui A, et al. Prognosis in hypertrophic cardiomyopathy: role of age, clinical, electrocardiographic and hemodynamic features. Am J Cardiol 1981;47:532-8.
2. Sigwart U. Nonsurgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211-4.
3. Knight C, Kurbann AS, Seggewiss H, et al. Nonsurgical septal reduction for hypertrophic obstructive cardiomyopathy: outcome in the first series of patients. Circulation 1997;95:2075-81.
4. Seggewiss H, Gleichmann U, Faber L, et al. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: acute results and 3-month follow-up in 25 patients. J Am Coll Cardiol 1998;31:252-8.
5. Lakkis NM, Nagueh SF, Kleiman NS, et al. Echocardiography-guided ethanol septal reduction for hypertrophic obstructive cardiomyopathy. Circulation 1998;98:1750-5.
6. Kazmierczak J, Kornacewicz-Jach Z, Kisly M, et al. Electrocardiographic changes after alcohol septal ablation in hypertrophic obstructive cardiomyopathy. Heart 1998;80:257-62.
7. Abuin G, Nieponice A. New findings on the origin of the blood supply to the atrioventricular node: clinical and surgical significance. Tex Heart Inst J 1998;25:113-7.
8. Bhargava B, Narang R, Aggarwal R, et al. Conduction blocks following transcatheter septal ablation for hypertrophic cardiomyopathy. Eur Heart J 1997;18(12):2011-2.
9. Bharati S, Levine M, Huang SK, et al. The conduction system in swine heart. Chest 1991;100(1):207-12.