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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執行單位：國立台灣大學醫學院內科

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計畫名稱：同步多保他命超音波心圖及鉈-201 電腦斷層造影於心臟移植病人冠心病之偵測及預後評估之價值

Diagnostic and Prognostic Value of Simultaneous Dobutamine Echocardiography and Thallium-201 SPECT for Noninvasive Assessment of Cardiac Allograft Vasculopathy

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一、中英文摘要

心臟移植病人之冠心病為換心人長期發病及死亡之重要原因。目前，該病之診斷主要依據侵襲性冠狀動脈造影及血管內超音波檢查。至於該病之非侵襲性檢查法，以 dobutamine 超音波心圖及鉈-201 心肌灌流檢查為最佳。本研究之目的，乃以冠狀動脈造影所見為診斷依據，探討上述二種非侵襲性檢查法於偵測換心人冠心病之靈敏度及特定度，以及對該病豫後評估之價值。

研究對象為 35 名換心人，接受同步 dobutamine 超音波心圖及鉈-201 心肌灌流攝影(二種檢查同時於同一病人進行)。另外，12 名左冠狀動脈阻塞病人及 12 名正常人亦被收入於本研究(當作控制組)。結果顯示：dobutamine 超音波心圖於偵測換心人冠心病之靈敏度及特定度，分別為 67% 及 94%，而鉈-201 心肌灌流之靈敏度及特定度分別為 100%及 78%。換心人鉈-201 心肌灌流之不均勻分數，於 1 年內如同正常人，但 1 年後，其不均勻分數逐年增加，尤以換心 3 年後分數之增加更多。簡言之，本研究顯示 dobutamine 超音波心圖與鉈-201 心肌灌流掃描於換心人冠心病之偵測上頗具價值。本研究亦顯示國人如同歐美洋人，換心後鉈-201 心肌灌流不均分數逐年增加，意涵冠心病之發生將逐年增多。

Abstract

Cardiac allograft vasculopathy (CAV) is the major cause of long-term morbidity and mortality in heart transplant recipients. At present, the mainstay of diagnosis of CAV consists of invasive coronary angiography and intravascular ultrasound. Recently, studies have pointed out that dobutamine echocardiography (DE) and ^{201}Tl SPECT may be the most promising of noninvasive methods for detection of CAV and for assessment of prognosis. Accordingly, the purposes of this study were to compare the relative merits of DE and dobutamine ^{201}Tl SPECT for the detection of CAV, and to assess the prognostic value of the two modalities.

The study population consisted of 35 heart transplant recipients in whom simultaneous DE and ^{201}Tl SPECT had been performed. Twelve patients with disease of the left anterior descending artery (LAD) and another 12 normal subjects were also enrolled for the evaluation of inhomogeneity of myocardial perfusion. The sensitivity and specificity for detecting CAV by DE were 67% and 94%, respectively. Using ^{201}Tl SPECT, they were 100% and 78%, respectively. The difference between the scores of transplant recipients surviving less than 12 months and those of control subjects was not statistically significant. One year after transplantation, the inhomogeneity score increased progressively. The scores of transplant patients in the second and third years after transplant were similar to those of

single-vessel LAD patients. Three years after transplant the scores were greatly increased. Thus, our data suggest that simultaneous DE and ^{201}Tl SPECT is of value in detecting CAV. The progressive nature of graft vasculopathy also exists in Chinese heart transplant recipients. The progressive Tl-201 abnormalities might be one of the early signs of graft vasculopathy.

二、緣由與目的

Cardiac allograft vasculopathy (CAV) is the major cause of long-term morbidity and mortality in heart transplant recipients (1-3). The presentation of the disease is frequently silent, resulting in delayed diagnosis. At present, the mainstay of diagnosis consists of invasive coronary angiography and IVUS (4). Angiography often underestimates the severity of the disease. IVUS has improved the early detection of CAV by directly imaging the coronary arterial wall (5-8). However, this technique is still invasive and requires cardiac catheterization for its implementation.

Dobutamine echocardiography (DE) has been reported to be one of the most promising of noninvasive methods for detection of CAV (9-15) and for assessment of prognosis (13-15). In addition, exercise thallium-201 (^{201}Tl) imaging has been reported to be of value in detecting CAV (16, 17). ^{201}Tl imaging also can provide prognostic information in heart transplant recipients (16, 18, 19). However, ^{201}Tl myocardial imaging with dobutamine stress in heart transplant recipients has not been examined. Recently, we have demonstrated that simultaneous DE and dobutamine ^{201}Tl SPECT is a valuable technique for the detection of nontransplant coronary artery disease (20) and for the evaluation of myocardial viability (21). Accordingly, the purposes of this study were to compare the relative merits of DE and dobutamine ^{201}Tl SPECT for the detection and prognostic assessment in patients with CAV.

三、方法

The study population consisted of 35 orthotopic heart transplant recipients (32 men, 3 women; aged 23-63 years) in whom simultaneous DE and ^{201}Tl SPECT, and coronary angiography had been performed. The procedure for simultaneous DE and ^{201}Tl imaging has been described previously in our laboratory (20). As described by Sawada et al (22), the left ventricle was divided into 16 segments for wall motion analysis. A normal response to dobutamine was defined as augmentation of systolic wall motion and myocardial thickening. Myocardial ischemia was considered present if new or worsening regional dyssynergy was induced during dobutamine stress. All SPECT images were interpreted qualitatively. The left ventricle was divided into 10 segments, as proposed by Iskandrian et al (23). Stress images were compared with redistribution images to evaluate the presence or absence of reversible or fixed defects. A ^{201}Tl scan with reversible and/or fixed defects was classified as abnormal.

Twelve patients with disease of the left anterior descending artery (LAD) and another 12 normal subjects were also enrolled for the evaluation of inhomogeneity of myocardial perfusion. The score of inhomogeneity was calculated as described by Puskás et al (24). CAV was diagnosed when a patient has angiographic changes of grade II or greater (11, 15).

Data are presented as mean ± SD. Paired continuous data were compared using the paired t test. χ^2 test was used to find significant association between categorical variables. Statistical significance was set at $p < 0.05$.

四、結果

Simultaneous DE and ^{201}Tl SPCET was performed 3-12 months after transplantation in 4 patients, 13-24 months in 14 patients, 25-36 months in 10 patients and after 3 years in 7 patients. Three patients (3 months, 25 months and 28 months after transplantation) had CAV on coronary angiography. DE identified CAV in 2 of the 3 patients but gave false positive results in another 2 patients. Thus, the sensitivity and specificity for detecting CAV

by DE were 67% and 94%, respectively. On the other hand, ^{201}Tl SPCET detected CAV in all the 3 patients but obtained false positive results in another 7 patients. Thus, using ^{201}Tl SPCET, the sensitivity and specificity for detecting CAV were 100% and 78%, respectively.

Table 1 shows the score percentage of inhomogeneity in control subjects, in patients with disease of the LAD, and in transplant recipients according to the duration after transplantation. The difference between score values of control subjects and transplant recipients surviving less than 1 year was statistically not significant. However, the difference between score values of control subjects and heart recipients more than 12 months after transplantation was highly significant ($p < 0.001$). There was a trend toward a greater increase in mean score over time. Three years after transplantation, the inhomogeneity score values much increased ($p < 0.05$ vs. any group).

Table 1. ^{201}Tl inhomogeneity score in normal subjects, in patients with LAD and in heart transplant recipients.

Study group	Score of inhomogeneity (%)	
	mean ± s.d.	Range
Controls (n = 12)	8.2 ± 3.5	3.3 - 14.4
LAD (n = 12)	16.3 ± 4.4*	8.9 - 24.4
Transplant recipients		
≤ 12 months (n = 4)	11.9 ± 3.6	8.9 - 15.6
13-24 months (n = 14)	16.8 ± 2.8*	13.3 - 21.1
25-36 months (n = 10)	17.3 ± 3.2*	13.3 - 23.3
> 36 months (n = 7)	22.2 ± 5.8*+	12.2 - 30.0

*$p < 0.001$ vs. controls. +$p < 0.05$ vs. any group.

五、討論

Verhoeven et al. (18) reported that probability of survival 5 years after cardiac transplantation was 97% for patients with normal exercise ^{201}Tl scan and only 26% for those with abnormal imaging at 1 year. Puskas et al (24, 25) disclosed that ^{201}Tl SPECT frequently revealed pathologic results in heart transplant recipients with normal coronary angiography. They observed that in the course of time, transplant recipients showed significantly increasing inhomogeneity score, despite reproducible normal angiographic findings. Similarly to their findings, in this study we found that there was a progressive increase in ^{201}Tl inhomogeneity score in heart transplant recipients as their surviving time increased. Puskas et al. suggested that ^{201}Tl abnormalities may be partly caused by small vessel alterations not identified by coronary angiography and IVUS. Therefore, the observed progressive ^{201}Tl abnormalities may be early signs of beginning CAV.

The incidence of transplant CAV was reported to be low in Chinese heart transplant recipients. Hsu et al (26) reported that the cumulative incidence of CAV detected by angiography in Chinese patients was only 2% at 1 year and also 2% at 2 and 4 years after transplantation, in contrast to 11%, 22% and 45%, respectively, in the Western series (4, 27). In this study we found that ^{201}Tl inhomogeneity score in transplant recipients surviving less than 1 year was not different from that in normal subjects. Thus, our data agree with the findings obtained by Hsu et al. (26) who observed that the incidence of CAV (by angiography) is lower in Chinese than in Caucasian. However, the progressive increase in inhomogeneity score with time observed in this series suggested that the progressive disease nature in CAV was the same in Chinese as well as in Caucasian.

六、結論與成果自評

In conclusion, this study demonstrates that simultaneous DE and ^{201}Tl SPECT is of value in detecting CAV. Mean ^{201}Tl inhomogeneity score in heart transplant recipient surviving less than 1 year is similar to that in normal subjects. One year after transplantation, the scores of inhomogeneity significantly increase over time. The observed progressive ^{201}Tl abnormalities probably may be one of the early signs of beginning graft vasculopathy. Long-term follow-up study is needed to explore this issue.

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