行政院國家科學委員會補助專題研究計畫成果報告

題目：循環附著分子及鉈-201 電腦斷層造影於預估心臟移植病人冠心病及冠事件之價值

Value of Circulating Adhesion Molecules and Thallium-201 SPECT for the Noninvasive Prediction of Transplant Coronary Artery Disease and Coronary Events

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執行期間：92 年 8 月 1 日至 93 年 7 月 31 日

計畫主持人：黃博昭

執行單位：國立台灣大學醫學院內科

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參與人員：吳彥雯、顏若芳、李啓明、王水深

執行機構及單位名稱：國立台灣大學醫學院內科、核子醫學部、外科部

一、中英文摘要

中文摘要

心臟移植病人冠心病爲換心人長期發病及死亡之重要原因。早期診斷及治療有助於換心人壽命之延長。新進研究顯示，血中循環附著分子如 sICAM-1, sVCAM-1 及 sE-selectin 之濃度，可能與換心人冠心病息息相關。另者，鉈-201 心肌灌流檢查可用來監視該病並評估其預後。本研究之目的，乃(1)探討循環附著分子之血中濃度與換心人冠心病之關聯性，及(2)探討 dobutamine 鉈-201 心肌異常灌流於換心人冠心病之診斷及豫後評估上之價值。

研究對象：25名換心人於心導管檢查當日抽取10 ml冠狀竇之血液做血漿附著分子之測定，以酵素放射免疫分析法(ELISA)測定之。本研究另選47名換心人接受dobutamine鉈-201心肌灌流檢查。當某一心肌節段鉈心肌灌流影像呈現可恢復性或永久性缺損，則被認爲異常。換心後病人定期於門診追蹤記錄其病程。

結果顯示：換心人中6名有冠心病sVCAM-1之血中濃度爲1015.9±457.3 ng/ml，無冠心病之血中濃度爲594.8±233.0 ng/ml ($p < 0.005$)，而sICAM-1及sE-selectin之血中濃度與換心人有無冠心病並無統計學上之差異。

另47名換心人中9名有冠心病，dobutamine鉈-201心肌灌流檢查之診斷靈敏度及特定度分別爲89%及71%。追蹤40.3 ± 21.9月之後，有4名因冠心病死亡。鉈-201心肌灌流異常≥6節斷者，其預後不良。

結論：冠狀竇sVCAM-1之血中濃度上升爲換心人冠心病之徵兆。Dobutamine 鉈-201心肌灌流檢查爲診斷換心人有無冠心病及評估其預後之非侵襲性良法。

Abstract

Circulating adhesion molecules have been implicated in the development of coronary allograft vasculopathy (CAV). We analyzed (s) soluble intercellular adhesion

molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), and sE-selectin levels from the coronary sinus of 25 cardiac allograft recipients. We found that sVCAM-1 significantly increased in patients with transplant vasculopathy compared with those without transplant vasculopathy, whereas sE-selectin and sICAM-1 did not. Therefore, increased coronary sinus levels of sVCAM-1 is a reliable marker in assessing cardiac transplant vasculopathy.

We also studied 47 patients at a mean of 34 ± 21 months after heart transplant with dobutamine ^{201}Tl SPECT. The sensitivity, specificity, positive and negative predictive values of SPECT for the detection of significant angiographic CAV were 89%, 71%, 42%, and 96%, respectively. Large reversible perfusion defects (≧ 6 segments) always indicated significant CAV. Over 40.3 ± 21.9 months after the first SPECT, one patient developed significant angiographic CAV and another 4 had cardiac death. Large reversible perfusion defect was a significant predictor of cardiac death ($p = 0.002$). Thus, dobutamine ^{201}Tl SPECT is a useful method for detecting patients with significant CAV and assessing prognosis.

二、緣由與目的

The expression of ICAM-1, VCAM-1 and E-selectin in capillaries correlates with the severity of cellular and humeral rejection, suggesting that monitoring cellular adhesion molecules (CAMs) may be a means of assessing rejection and response to therapy.[1] However, the correlation between levels of CAMs and cardiac rejection is still inconclusive.[2-4]

On the other hand, previous studies have shown that stress ^{201}Tl imaging is of value in detecting transplant coronary artery disease (CAD). [5,6] We [7] and others [8] have found that there is a progressive increase in ^{201}Tl inhomogeneity score in heart transplant recipients as their survival time increased. We postulated that CAMs may add to the value of ^{201}Tl SPECT in predicting transplant arteriopathy.

Accordingly, the purposes of this study are (1) to assess the relationship of CAMs (sICAM-1, sVCAM-1, sE-selectin) with transplant CAD, and (2) to test whether patients with higher concentration of CAMs alone, or in combination with ^{201}Tl perfusion abnormalities, are at increased risk of future transplant CAD.

三、方法

We recruited 25 cardiac transplant recipients (22 men and 3 women; mean age, 52±11 years) for study of CAM. Just before patients underwent endomyocardial biopsy, 10 ml blood was taken from the coronary sinus to measure sE-selectin, sICAM-1, and sVCAM-1 using enzyme-linked immunosorbent assay.[9]

We graded coronary lesions as follows: grade I, normal angiograms; grade II, luminal irregularities, diameter reduction < 30%; grade III, diameter reduction 30-49%; grade IV, diameter reduction ≥ 50% and/or diffuse narrowing of small vessels.[10] Transplant vasculopathy was diagnosed as angiographic changes of grade III or IV.

We also studied 47 patients at a mean of 34 ± 21 months after heart transplant with dobutamine ^{201}Tl SPECT, which was performed as previously described.[11]

Data are presented as mean ± SD. Student's t-test, chi-square analysis and one-way analysis for variance were performed when appropriate.

四、結果

Six of 25 patients had angiographically documented transplant vasculopathy. sVCAM-1 levels significantly elevated in patients with transplant vasculopathy compared to those without (1015.9 ± 457.3 vs 594.8 ± 233.0 ng/ml, $p < 0.005$). Levels of sE-selectin and sICAM-1 were similar in patients with and without CAV.

Significant angiographic CAV was detected in 9 of the 47 cardiac recipients. The sensitivity, specificity, positive and negative predictive values of SPECT for the detection of significant angiographic CAV were 89%, 71%, 42%, and 96%, respectively. Large reversible perfusion defects (≧ 6 segments) always indicated significant CAV. Over 40.3 ± 21.9 months after the first SPECT, one patient developed significant angiographic CAV and another 4 had cardiac death. Large reversible perfusion defect was a significant predictor of cardiac death ($p = 0.002$).

五、討論

Previous studies have shown an association between the degree of macrophage accumulation and expression of VCAM-1 on atherosclerotic plagues,[12] and the extent of atherosclerosis seemed to correlate with sVCAM-1 but not with sP-selectin, sE-selectin or sICAM-1.[13] Our data confirmed that elevated sVCAM-1 was a good marker of transplant vasculopathy and suggested that monitoring VCAM-1 might be helpful in the detection of patients at higher risk to develop transplant vasculopathy.

Labarrere et al. found that increased levels of sICAM-1 was related to the subsequent development of transplant vasculopathy.[3] However, in this study the coronary sinus levels of sICAM-1 in patients with transplant vasculopathy were not significantly increased. Our results were not totally unexpected, as other study[4] also showed lack of elevation of sICAM-1 in patients with chronic cardiac vasculopathy.

Exercise ^{201}Tl myocardial perfusion imaging has been used to identify CAV with sensitivity varying from 67% to 78%, and specificity ranging from 33% to 100%. [14-16]

To date, there has been no data regarding the accuracy of dobutamine ^{201}Tl SPECT in the diagnosis of significant CAV. The sensitivity of 89% obtained in our patients was as high as that reported by Elhendy et al. using dobutamine tetrafosmin myocardial imaging.[17] The specificity of 71% in this series was comparable with previous observations using either exercise or dipyridamole as stress agent.

Verhoeven et al.[18] studied patients with exercise or dipyridamole planar ^{201}Tl imaging and found that abnormal stress ^{201}Tl scan was significantly associated with poorer subsequent survival. Our data showed that the presence of large reversible perfusion defects was a significant predictor to subsequent cardiac mortality.

六、結論及成果自評

We concluded that increased coronary sinus levels of sVCAM-1 is a reliable marker in assessing cardiac transplant vasculopathy, and that dobutamine ^{201}Tl SPECT is a useful method for detecting patients with significant CAV and assessing prognosis.

To the best of our knowledge, this study is the first to analyze the CAM levels in coronary sinus to reflect the immune activation state of the heart. This study is also the first using dobutamine ^{201}Tl SPECT to detect the presence of CAV and assess prognosis.

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