行政院國家科學委員會專題研究計畫 成果報告

用杜卜勒超音波,超音波組織特性圖與鉻-99 同位素心室造 影來分析高血壓病患舒張功能之變化-與心肌纖維化的血

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一、中文摘要

越來越多的研究顯示心肌纖維化在高血壓 心臟變化中扮演了相當重要的角色。利用 免疫組織化學呈相法顯示在高血壓心臟病 的患者,其心臟間質及冠狀動脈週圍有大 量的第一類及第三類纖維膠原沉積。大量 的心臟纖維化會導致心室舒張功能異常。 在各種人體有關心臟纖維化的病理研究中 發現: 心肌細胞的超音波反射度與膠原堆 積的量有相當程度的關聯性。因此對研究 心肌纖維化而言; 加成性超音波逆行散射 (週期變化與波幅大小的改變)便成為一種 優良的非侵襲性工具。另一方面,膠原纖 維原分解的過程中會釋放一些物質如第一 類膠原纖維原碳基端分解物(PIP)、第三類 膠原纖維原胺基端分解物(PIIIP)至血清 中。據研究顯示,這些血清中的膠原纖維 分解物與心肌纖維化有關。在肝功能正常 的前提下,這些血清中的膠原纖維分解物 與組織中膠原纖維製造有量化性的相關。

因此我們設計這個研究;利用用杜卜勒超 音波,超音波組織特性圖與鎝-99 同位素心 室造影來分析高血壓病患舒張功能之變 化; 並分析這些舒張功能變化與心肌纖維 化的血清標記之相關。這個研究目的有(1) 定量這些病患血清中的膠原纖維分解物 (PIP 與 PIIIP)之數值; (2) 比較這些病患 左心室加成性超音波逆行散射(週期變化 與波幅大小的改變)、杜卜勒超音波左心 室舒張功能評估「等容性左心室舒張時間 (isovolumetric relaxation time); 二尖瓣血 流速度與減速時間 (mitral flow velocities and deceleration time):肺靜脈血流的速度 與速度時間積分面積等與血清中的膠原纖 維分解物(PIP 與 PIIIP)之相關; (3) 比較病 患鎝 99 心室造影舒張功能異常與血清中

的膠原纖維分解物(PIP 與 PIIIP)之相關。 共有 22 名高血壓病患進入本研究。將 PINP 以 35ug/l 作界線將病人分成兩組(第 一組 7 人,其 PINP 濃度為 24±8 ug/l、第 二組 15 人,其 PINP 濃度為 66±17 ug/l) 來分析舒張功能檢查的結果。PIIINP(3.8± 1.4vs 4.8±1.5 ug/l)、左心室大小(LVEDD 40±6 vs 43±4 mm/ LVESD 25±4 vs 26±3 mm)、二尖瓣血流參數(E/A ratio 0.7±0.2 vs 0.8±0.2; deceleration time 229±59 ms vs 217 ± 49ms)、肺靜脈血流參數 (retrograde A wave 32±4 cm/s vs 37±7 cm/s; 收缩血流 59±5 cm/s vs 67±14 cm/s; 舒張血流 37±6 cm/s vs 46±10 cm/s)、等容性左心室舒張時間 86±14 ms vs 84±17 ms、Tei index (0.5±0.0 vs 0.5± 0.1)、超音波組織特性圖 (amplitude 6.7± 3.1 vs 7.4±2.2db)等在兩組間均無差異 核 醫檢查則有明顯差異: peak filling rate of LV (3.4±0.8 vs 2.5±0.6 EDV/s; p=0.009); time to peak filling rate of LV 272±130 ms vs 176±72 ms; p<0.05]。PIIINP 則與 舒張功能無相關 結論: 高血壓病患超音波 逆行散射波幅、杜卜勒血流參數與膠原纖 維分解物 PINP 與 PIIINP 無明顯相關,但 鎝-99 心肌造影之舒張功能異常參數(peak filling rate of LV; time to peak filling rate of LV)與膠原纖維分解物 PINP 有相關而與 PIIINP 無關。

關鍵詞:加成性超音波逆行散射;血清中的膠原纖維分解物; 鎝-99 心肌造影;高血壓性心臟病之纖維化

Abstract

A growing body of evidence indicates that myocardial fibrosis is one of the key

pathologic features of myocardial remodeling in hyperensive heart disease. An exaggerated accumulation of collagens type I and type III within the myocardial interstitium and surrounding intramural coronary arteries and arterioles has been evidenced patients immunohistologically in with hypertensive heart disease. Myocardial fibrosis predisposes to diastolic dysfunction of ventricle which, in turn, confer increased risk of adverse cardiovascular events to patients with hypertension. To determine the extent of collagen accumulation in tissue may be relevant in assessing the clinical outcome of these patients and in designing strategies to prevent its appearance or even to cause its regression. Studies performed in human with different pathologic conditions involving myocardial fibrosis have shown a promising correlation between echo-reflectivity and histologically assessed collagen content. Therefore, cyclic variation of in returning ultrasound signal intensity (cyclic variation of integrated backscatter) turns to be a non-invasive tool for measurement of myocardial fibrosis. On the other hand, serum procollagen type I carboxy-terminal peptide (PIP) and procollagen type III amino terminal peptide (PIIIP) have been related to myocardial fibrosis. Serum PIP and PIIIP concentration can be considered as a useful marker of myocardial collagen type I and III synthesis in conditions of preserved liver function. Therefore, we assessed the diastolic dysfunction of hypertensive patients. The parameter for diastolic dysfunction included mitral flow, pulmonary venous flow, Tei index, integrated backscatter and Tc-99m ventricular function assay. This prospective study was designed (1) to analyze the relation between myocardial integrated backscatter and serum markers (PIP and PIIIP) of myocardial fibrosis (2) to analyze the relation between myocardial Tc-99m imaging and serum markers (PIP and PIIIP) of myocardial fibrosis (3) to analyzed the relation among mitral flow, pulmonary venous flow and Tei index and serum markers (PIP and PIIIP) of myocardial fibrosis. A total of 22 hypertensive patients were enrolled into this study. Using 35ug/l of PINP, we divided

these patients into 2 groups: group 1 (7 patients with mean PINP 24 ug/l) and group 2 (15 patients with mean PINP 66 ug/l). There were no significant differences between these 2 groups: $PIIINP(3.8 \pm 1.4 vs)$ 4.8 ± 1.5 ug/l),left ventricular (LV)end-diastolic dimension 40±6 vs 43±4 mm; LV end-systolic dimension 25±4 vs 26±3 mm, mitral E/A ratio 0.7 ± 0.2 vs 0.8 ± 0.2 , deceleration time of mitral flow 229±59 ms vs 217 ± 49ms, retrograde A wave of pulmonary venous flow 32±4 cm/s vs 37±7 cm/s, systolic flow of pulmonary venous flow 59±5 cm/s vs 67±14 cm/s, diastolic flow of pulmonary venous flow 37±6 cm/s vs 46±10 cm/s, isovolumetric relaxation time 86±14 ms vs 84±17 ms, Tei index 0.5±0.0 vs 0.5± 0.1, amplitude of cyclic variation of integrated backscatter 6.7±3.1 vs 7.4±2.2db. However, there were significant differences between peak filling rate of LV (3.4±0.8 vs 2.5 ± 0.6 EDV/s; p=0.009) and time to peak filling rate of LV 272±130 ms vs 176±72 ms; p<0.05].No siginificant association was observed for PIIINP and diastolic dysfunction of LV. In conclusion, ultrasound parameters of diastolic dysfunction of left ventricle are not related to PINP and PIIINP in hypertensive patients. Peak filling rate and time to peak filling rate are associated with PINP rather than PIIINP in such patients.

KeyWords:Integratedbackscatter;Tc99mventriculography;procollagen type I and III peptide; myocardialfibrosis; hypertensive heart disease

二、緣由與目的

In addition to left ventricular hypertrophy, interstitial and perivascular fibrosis also account for loss of tissue homogeneity and pathological cardiac remodeling in hypertensive patients. An exaggerated accumulation of collagens type I and type III within the myocardial interstitium and surrounding intramural coronary arteries and arterioles has been evidenced immunohistologically patients in with hypertensive heart disease.¹ Myocardial collagen volume fraction (CVF) have been reported to be increased in hypertensive patients.²⁻⁵ Chronic pressure overload stimulates both procollagen gene expression and collagen protein synthesis leading to excessive collagen deposition and fibrosis.⁶Ouerejeta et al. characterized three histologic grades of interstitial fibrosis in biopsy myocardial tissue obtained from patients with essential hypertension: 11% of patients exhibited minimal fibrosis (CVF< 2%), 58% of patients exhibited moderate fibrosis (CVF from 2-8%), and 31% of patients exhibited severe fibrosis (CVF >8%).⁵ Both systolic and pulse pressure were higher in the group of patients with severe fibrosis compared with the other 2 groups.

Myocardial fibrosis predisposes to ventricular dysfunction and diminished coronary reserve, which, in turn, confer increased risk of adverse cardiovascular events to patients with hypertension. An inverse correlation exists between CVF and Doppler mitral A wave deceleration time in hypertensive patients.⁷ An inverse relation has also been found between left ventricular ejection fraction and CVF in hypertensive patients.⁸ Laviades et al. reported that a twoto threefold increase in CVF adversely influences diastolic dysfunction, and a four-fold or more rise in CVF is associated with a further rise in diastolic stiffness and a decline in systolic dysfunction.⁹ On the other hand, it is increasingly recognized that patients with hypertensive heart disease have symptoms and signs of myocardial ischemia despite angiographically normal coronary arteries, and it was related to impaired coronary flow reserve.¹⁰ Schwartzkopff et al. have demonstrated that total and perivascular CVF correlated with the increased coronary flow resistance in hypertensives with reduced coronary flow reserve.¹¹ The overall amount of perivascular fibrosis is also a limiting factor for vascular distensibility in hypertensive heart disease.¹²

To determine the extent of collagen accumulation in tissue may be relevant in assessing the clinical outcome of these patients and in designing strategies to prevent its appearance or even to cause its regression. Although the endomyocardial biopsy procedure is a simple and relative safe

procedure, this is an invasive methodology with obvious limitations for wide-scale application. Recently, alternations in the patterns of myocardial acoustic reflectivity have been described in patients with hypertensive heart disease, especially in those with severe hypertrophy.^{4,13} Ciulla et al. report a direct correlation between CVF and echo amplitude in patients with hypertensive heart disease.⁴ Studies in humans with different pathologic conditions involving myocardial fibrosis have shown a promising correlation between echo-reflectivity and histologically assessed collagen content.¹⁴⁻¹⁷ Therefore, cyclic variation of returning ultrasound signal intensity [cyclic variation of integrated backscatter (IBS)] turns to be a non-invasive tool for measurement of myocardial fibrosis.

Fibrillar collagen type I is synthesized in the fibroblasts as procollagen type I. After procollagen type I has been secreted into the extracellular space, the propeptides (procollagen type I carboxy-terminal peptide, PIP) are removed by specific proteinase, allowing integration of the collagen helix into the growing fibril.¹⁸ Procollagen type III amino terminal peptide (PIIIP) is also formed and released into the blood during the similar process. Several clinical observations have demonstrated that high serum levels of the PIP and PIIIP measured bv radio-immunoassay reflect continuous tissue fibrosis.¹⁸⁻²⁰ Serum PIP and PIIIP concentrations are increased in hypertensive patients.²¹ An inverse correlation is found between serum PIIIP and diastolic mitral flow velocity.²¹ Serum PIP concentrations increase in parallel with the left ventricular mass index and severity of ventricular arrhythmia.²¹ Serum PIP concentration correlates directly with CVF in patients with disease.⁵ hypertensive heart A strong association between also exists treatment-induced changes in CVF and treatment-induced changes in serum PIP.²² Therefore, measurements of serum PIP and PIIIP concentrations provide indirect diagnostic information on the development of collagen type I and III-dependent myocardial fibrosis in patients with hypertensive heart

disease.18

This prospective study was designed (1) to analyze the relation between myocardial integrated backscatter and serum markers (PIP and PIIIP) of myocardial fibrosis (2) to analyze the relation between myocardial Tc-99m imaging and serum markers (PIP and PIIIP) of myocardial fibrosis (3) to analyzed the relation among mitral flow, pulmonary venous flow and Tei index and serum markers (PIP and PIIIP) of myocardial fibrosis.

三、結果

A total of 22 hypertensive patients were enrolled into this study. Using 35ug/l of PINP, we divided these patients into 2 groups: group 1 (7 patients with mean PINP 24 ug/l) and group 2 (15 patients with mean PINP 66 ug/l). There were no significant differences between these 2 groups: PIIINP(3.8±1.4vs 4.8±1.5 ug/l),LVEDD 40±6 vs 43±4 mm; LVESD 25±4 vs 26±3 mm, mitral E/A ratio 0.7 ± 0.2 vs 0.8 ± 0.2 ; deceleration time of mitral flow 229 ± 59 ms vs 217 ± 49 ms, retrograde A wave of pulmonary venous flow 32±4 cm/s vs 37±7 cm/s; systolic flow of pulmonary venous flow 59±5 cm/s vs 67±14 cm/s; diastolic flow of pulmonary venous flow 37±6 cm/s vs 46±10 cm/s, isovolumetric relaxation time 86±14 ms vs 84±17 ms, Tei index $(0.5 \pm 0.0 \text{ vs } 0.5 \pm 0.1)$, amplitude of cyclic variation of integrated backscatter 6.7± 3.1 vs 7.4 ± 2.2 db. However, there were significant differences between peak filling rate of LV $(3.4 \pm 0.8 \text{ vs } 2.5 \pm 0.6 \text{ EDV/s};$ p=0.009) and time to peak filling rate of LV 272±130 ms vs 176±72 ms; p<0.05]. In conclusion, ultrasound parameters of diastolic dysfunction of left ventricle are not related to PINP and PIIINP. Peak filling rate and time to peak filling rateof LV are associated with PINP rather than PIIINP.

四、討論

PIIINP and LV diastolic dysfunction in hypertensive patients

The PIIINP is an extension peptide of procollagen type III, which is cleaved off

during conversion from type III procollagen to type III collagen. PIIINP reflects myocardial fibrosis, which is higher in the tissue of dilated and dysfunctional left ventricles.¹⁹⁻²⁰Importantly, increased PIIINP concentrations account for decreased survival in patients with DCM. ¹⁹ In patients with dilated cardiomyopathy, restrictive mitral pattern is also associated with higher PIIINP and worse prognosis. ²¹ However, in our hypertensive patients with normal systolic function of LV, there was no association of PIIINP and diastolic dysfunction of LV.

PINP and LV diastolic dysfunction

Diastolic dysfunction has been reported to be related to PINP in patients with hypertrophic $(HCM)^{22}$ cardiomyopath Increased collagen subtype I is a predictor of diastolic as well as systolic dysfunction under exercise in patients with HCM after successful myectomy.²³ transaortic subvalvular Pressure-overload ventricular left hypertrophy (LVH) is characterized by an increase in myocyte size and fibrosis. This LVH pattern is different from HCM. There was no demonstrable relationship between plasma collagen type Ι and echocardiographic findings (isovolumetric relaxation time, E:A ratio, and E wave deceleration times) in hypertensive patients.²⁴ In our study, there was also no significant association between PINP and echocardiographic parameters of diastolic dysfunction. On the other hand, the PINP was significant associated with peak filling rate and time to peak fillng rate of LV. The patients in group II had shorter time to peak filling rate and lower peak filling rate of LV.

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