行政院國家科學委員會專題研究計畫成果報告

Preparation of NSC Project Reports

† 八十六年度及以前的一般國科會專題計畫(不含產學合作研究計畫)亦可選擇適用，惟較特殊的計畫如國科會規劃案等，請先洽得國科會各學術處同意。

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主持人：吳美環　台大醫學院小兒科

一、中文摘要

地中海貧血症病兒因需反覆輸血易導致鐵質堆積，近年雖有排鐵劑治療之引進，但鐵質沉積於心臟造成的心肌症及心律不整仍是地中海貧血症病兒之重要死因(63%)。地中海貧血症病兒之心肌症，初期雖以舒張功能受損為主，末期則合併收縮功能不良而導致心臟衰竭，傳統心衰竭藥物(包括毛地黃、利尿劑及ACE拮抗劑等)效果並不理想。

Carvedilol為第二代之β拮抗劑，其接受器之拮抗作用依序為β1>α1>β2。由於對α接受器亦有拮抗作用可降低血管阻力，可於心衰竭時投以。此外，Carvedilol亦有明顯之抗氧化能力。已有許多臨床報告證實carvedilol對慢性心衰竭的療效並通過認證。

因為鐵質沉積造成之心肌症其機轉與鐵質可能誘發free radical產生有關，因此我們推想carvedilol由於有抗氧化作用，且有改善心衰竭之作用應有助於鐵沉積心肌症之症狀緩解。我們的初步經驗相當令人振奮。初例為20歲地中海症女孩，因反覆輸血已有心肌功能受損，但於接受carvedilol治療後，心肌功能有大幅改善。由於此病人臨床上並無心跳加速等交感神經亢奮之現象，carvedilol直接對心臟的影響是很可能存在的。

本實驗利用確立的離體心臟模式來探討傳導系統之電生理特性之變化及再灌流不整脈之誘發。結果顯示Carvedilol確能直接改變心電生理特性，可縮短房室結之傳導及心室組織之抑阻期。對於再灌流不整脈之誘發概率亦能略減少(100%降到81%)。此外並能停止再灌流不整脈，但最多只有50%效力(1.5μM與5.4μM皆然)。至於細胞內鐵質負荷後所導致的心電生理變化為心週期延長及房室間傳導性與心室組織抑阻期之縮短，而carvedilol之添加並無法顯著更改其鐵質負荷導致之變化。而細胞外鐵質負荷後，其心週期亦延長，而房室傳導也延長。由以上之結果我們可推論carvedilol除其原本之強β弱α抗拮劑之作用外，亦有直接之電生理效應，急性鐵質負荷可能改變心電生理特性，但carvedilol並無效改變急性鐵質負荷所導致之改變。

二、ABSTRACT

Background. Myocardial iron storage along with the secondary cardiomyopathy is an unavoidable problem in thalassemia patients and remains the most common cause of death. Conventional treatment for the heart failure is helpful but still unsatisfactory. Carvedilol, a "third generation" ß blocking agent that at

therapeutic doses blocks all three adrenergic receptors, with a rank order of potency of $ß_1$> α_1 > $ß_2$. Because of its α-blocking effect, carvedilol is a moderate vasodilator on acute administration and therefore has a good initial tolerability in patients with heart failure. Besides, carvedilol has been shown as a strong antioxidant. Since increased levels of redox-active iron with free radical production may be the mechanism of tissue damage in thalassemia patients, we hypothesize that carvedilol will be helpful for the thalassemia patients, by the attenuation of enhanced sympathetic activity as well as the attenuation of free radical damage in iron-loaded hearts.

Methods. The direct modification by various interventions on cardiac conduction system was performed by intracardiac recording and stimulation in isolated, Langendorff perfused hearts. The and proarrhythmic potential was assessed by the incidence of ischemia/reperfusion arrhythmias after various interventions.

Results. Carvedilol may directly shorten progressively the conduction through the AV node as well as the ventricular refractory period (1.5 and 4.5 μM). However, theses changes were irreversible. As to the conduction through the atrial, His-Purkinje system and their refractoriness were not significantly modified by carvedilol Intracellular iron-load by co-addition with pyrithione 10 μM might significantly prolong the basic cycle length, shorten the wenckebach cycle length and the ventricular effective refractory period. Furthermore, the addition of carvedilol failed to convert these changes. Extracellular iron-load induced by co-addition of the ADP and Fe might prolong the basic cycle length and the conduction through the AV node (AH interval). Carvedilol can modestly convert the ventricular tachyarrhythmias induced by ischemia-reperfusion. At 1.5 μM and 4.5 μM, carvedilol could covert half of the reperfusion arrhythmias. Pretreatment by carvedilol (1.5 or 4.5 μM) could decrease the incidence of reperfusion arrhythmias from 100% (5/5) to 81% (9/11).

Conclusions. Direct electropgysiological effects of carvedilol and the potential of ameliorating ischemia-reperfusion arrhythmias had been documented. Acute iron-load may alos alter the elctrophysiological properties of the heart. However, carvedilol could not convert these changes.

三、緣由與目的

The fate of thalassemia major patients has substantially been improved during the past 15 years following the introduction of high-controlled regimens of blood transfusion and chelation therapy.[1] However, myocardial iron storage is still unavoidable and remains the most common cause of death (63%).[2-3] At the end stage, patients are usually die of intractable heart failure and sudden (arrhythmic) death. Such thalassemia-related cardiomyopathy heart is characterized by predominant diastolic dysfunction in the early stage and by systolic dysfunction in the late stage.[4-6] Our previous study has found that prognostic values of the left ventricular diastolic index.[6] Furthermore, the coexistence of pulmonary bed alteration may lead to right ventricle surcharge and aggravate the heart failure. Conventional treatment for the heart failure in thalassemia-related cardiomyopathy include: digoxin, diuretics, and angiotensin converting enzyme inhibitor. However, the result is still unsatisfactory.[1]

Carvedilol, a "third generation" ß-blocking agent that at therapeutic doses blocks all three adrenergic receptors, with a rank order of potency of $ß_1$> α_1 > $ß_2$.[7] Because of its α-blocking effect, carvedilol is a moderate vasodilator on acute administration and therefore has a good initial tolerability in patients with heart failure. Besides, carvedilol

has been shown as a strong antioxidant.[8] Clinical benefits have been well documented in patients with chronic heart failure from several multicenter clinical trials and hence carvedilol had been approved for the treatment of heart failure.[9-12]

Our previous observation in thalassemia patients has indicated the prognostic values of echocardiography, including the diastolic and systolic parameters.[6] The heart failure may be improved by conventional medications, but the heart failure progressed. Since increased levels of redox-active iron with free radical production may be the mechanism of tissue damage in thalassemia patients, we propose that carvedilol will be helpful for the thalassemia patients, not only by the attenuation of enhanced sympathetic activity but also the attenuation of free radical damage in iron-loaded hearts.

四、結果

1. Direct electrophysiological effects
   A). Carvedilol:
   Carvedilol can cause progressively shortening of the conduction through the AV node. The ventricular refractory period was also significantly shortened (1.5 and 4.5 μM). However, theses changes were irreversible. (Table 1) As to the conduction through the atrial, His-Purkinje system and their refractoriness were not significantly modified by carvedilol
   B). Intracellular iron-load: Intracellular iron-load by co-addition with pyrithione 10 μM had been shown that the intracellular Fe load may significantly prolong the basic cycle length, shorten the wenckebach cycle length and the ventricular effective refractory period. Furthermore, the addition of carvedilol failed to convert these changes.
   C). Extracellular iron-load: Extracellular iron-load was induced by co-addition of the ADP and Fe. The results showed that the extracellular iron-load may significantly prolong the basic cycle length and the conduction through the AV node (AH interval).
2. Antiarrhythmic effects (Ischemia-reperfusion model)
   A). Carvediolol: Carvedilol can modestly convert the ventricular tachyarrhythmias induced by ischemia-reperfusion. Carvedilol at 0.5 μM failed to convert the tachyarrhythmias , at 1.5 μM, carvedilol converted one out of two induced tacharrhythmias and at 4.5 μM carvedilol could only convert 3 out of 6 induced ventricular tachyarrhythmias.

B). Pretreatment by carvedilol (1.5 or 4.5 μM) could decrease the incidence of reperfusion arrhythmias from 100% (5/5) to 81% (9/11) (No statistical significance).

五、討論

Direct electrophysiological effects had been well shown in this study. However, the antiarrhythmic efficacy was only fair. Pretreatment with carvedilol provided the hearts only weakly against the development of ischemia-reperfusion arrhythmia. Acute cellular iron load mal alter the elctrophysiological properties of the hearts. However, carvediolol failed to modify these changes. These data suggested a modest weak direct antiarrhythmia efficacy of carvedilol other than its beta-blocking activities. The effects of acute iron load could not be prevented by carvedilol. Whether carvedilol may protect the hearts from chronic iron load remained unanswered. Further investigation is mandatory.

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