Prognostic Value of High-Sensitivity C-reactive Protein in Patients with Chronic Heart Failure

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XUE ET AL.: ***Prognostic Value of High-Sensitivity C-reactive Protein in Patients with Chronic Heart Failure.*** ***Objectives:*** *To determine whether High-Sensitivity C-reactive Protein (hsCRP) has Prognostic value in patients with chronic heart failure.* ***Methods:*** *Serum hsCRP levels were measured with high-sensitivity assay (IMMAGE Immunochemistry Systems) in 128 patients with CHF and 25 healthy control subjects. Cardiac troponin T (TNT) was measured by Electrochemiluminescence immunoassay on Elecsys1010 automatic analyzer. Cardiac events were defined as cardiac death and rehospitalization because of worsening heart failure during a mean follow up period of 378±26 days.* ***Results:*** *Circulating levels of hsCRP and TNT were significantly higher (3.85±4.25 mg/L, 0.21±0.15 mg/L, respectively) in patients with CHF than in 25 healthy people ($p<0.01$, $p<0.01$, respectively) and increased with severity of CHF. During a mean follow up period of 378±26 days, forty-two (32.8%) of the 128 patients had cardiac events. Levels of hsCRP and TNT were significantly higher ($p<0.001$, $p<0.001$, respectively) and left ventricular ejection fraction (LVEF) was significantly lower ($p<0.01$) in patients with cardiac events than in patients without cardiac events. When multivariate Cox proportional hazards analysis was performed, we could find that hsCRP, TNT, and LVEF were independent significant predictors of cardiac events in patients with CHF. (hsCRP: hazard ratio[HR], 3.81; 95%CI, 2.14-9.35; P=0.024; TNT: HR, 2.61; 95%CI, 1.96-4.31; P=0.012; LVEF: HR, 3.52; 95%CI, 2.36-10.37; P=0.024). A positive correlation was observed between hsCRP and TNT ($r=0.493$, $p<0.01$). A negative correlation was observed between hsCRP and LVEF ($r=-0.354$, $p<0.01$).* ***Conclusion:*** *Serum hsCRP concentrations were elevated in patients with CHF and increased with severity of CHF. It was an independent significant predictor of cardiac events in patients with CHF. (J HK Coll Cardiol 2004;12:64-69)*

Congestive, C-reactive protein, heart failure, prognoses

摘要

目的：觀察高敏C-反應蛋白（hsCRP）對慢性充血性心力衰竭病人是否有預後判斷價值。**方法：**本研究包括128例慢性充血性心力衰竭（CHF）病人和25例健康人。應用高敏法（IMMAGE Immunochemistry Systems）檢測病人及健康對照組血清hsCRP，同時應用電化學發光免疫分析法檢測肌鈣蛋白T（TNT），並與hsCRP比較。隨訪病人，觀察其預後。心臟事件定爲隨訪期內（378 ± 26天）心源性死亡或因心力衰竭惡化再住院。**結果：**病人血清hsCRP 和TNT濃度(分別爲3.85 ± 4.25 mg/L, 0.21 ± 0.15 mg/L)高於健康對照組($p<0.01$，$p<0.01$)，病情越嚴重其濃度越高。在隨訪期內（378 ± 26天），128例病人中有42人(32.8%)發生心臟事件。發生心臟事件的病人，血清hsCRP和TNT濃度高於未發生心臟事件的病人($p<0.001$，$p<0.001$)，左室射血分數（LVEF）低於未發生心臟事件的病人($p<0.01$)。應用多變量Cox風險比例模型分析，發現hsCRP， TNT和 LVEF是心力衰竭病人獨立的預後判斷指標(hsCRP：風險比[HR]，3.81；

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95%CI，2.14-9.35；*P*=0.024；TNT：HR，2.61；95%CI，1.96-4.31；*P*=0.012；LVEF：HR，3.52；95%CI，2.36-10.37；P=0.024)。CHF病人血清hsCRP 和TNT存在正相關 (r=0.493，*p*<0.01)。hsCRP 和 LVEF存在負相關 (r=-0.354，*p*<0.01)。**結論：**慢性充血性心力衰竭病人血清hsCRP濃度升高，病情越嚴重其濃度越高。hsCRP是心力衰竭病人獨立的預後判斷指標。

關鍵詞：充血性　C-反應蛋白　心力衰竭　預後

Introduction

The serum concentration of C-reactive protein (CRP) is mildly elevated in patients with chronic congestive heart failure (CHF). Standard assay for CRP lack the sensitivity within the low reference range and thus cannot be used effectively for routine clinical risk prediction. Our study was aimed at investigating high-sensitivity assay of CRP (hsCRP), a marker of systemic inflammation, in the context of heart failure, and to determine if it has prognostic value in patients with CHF.

Methods

Patients

A total of 128 patients (Chinese) with chronic heart failure were enrolled in this study. The diagnosis of chronic heart failure (CHF) was based on the criteria below produced by the European Society of Cardiology:[1]

1. Symptoms of heart failure (at rest or during exercise)
2. Objective evidence of cardiac dysfunction (at rest)
3. Response to treatment directed toward heart failure (in cases where the diagnosis is in doubt)

The characteristics of patients with CHF were summarized in Table 1.

All patients had a left ventricular ejection fraction (LVEF) <40% or had a mean left ventricular end-systolic dimension >55 mm by transthoracic echocardiography. Ischemic CHF was diagnosed by coronary angiography (>50% luminal diameter narrowing in at least 1 major epicardial coronary artery) or by the history of documented myocardial infarction.

Table 1. The characteristics of patients with CHF

No. of patients	128
Age (y)	62±15
Sex M/F	79/49
No. of diabetics	19
No. of smokers	35
Cause of CHF	
Ischemic CHF	75
Non-Ischemic CHF	53
NYHA n (%)	
Class II	57 (44.5%)
Class III	40 (31.3%)
Class IV	31 (24.2%)
Left ventricular ejection fraction	
All patients with CHF	0.37±0.11
Ischemic CHF	0.36±0.09
Non-Ischemic CHF	0.33±0.08
Class II	0.36±0.12
Class III	0.27±0.12
Class IV	0.19±0.13

Non-Ischemic CHF was caused by primary dilated cardiomyopathy (26 patients), valvular heart disease (15 patients), systemic hypertension (12 patients). We excluded patients with clinical or laboratory evidence of systemic infection, myocardial infarction within 8 months, pericarditis, cor pulmonale, inflammatory illness such as arthritis or connective tissue diseases, any malignancy tumor.

Control population consisted of 25 healthy Chinese people (men 15, women 10, mean age 59±16 years old). Blood samples from patients were obtained on the first day of admission. Control blood samples from 25 healthy people were obtained at fasting condition. Blood samples were allowed to clot for 30 minutes at room temperature and were centrifuged for 5 minutes. All blood samples were measured without

frozen within 3 hours after blood samples were obtained. All patients were followed up by telephone, or through regular outpatients visits, or when they were rehospitalized. Mean follow up period was 378±26 days. Cardiac events was defined as cardiac death and rehospitalization because of worsening heart failure.

Measurements of hsCRP and TNT

hsCRP was measured by immunoassay with an autoanalyzer (IMMAGE Immunochemistry Systems, Beckman Coulter, California). The intra-assay and inter-assay coefficients of variation for hsCRP were 5% and 10%, respectively. TNT was measured by Electrochemiluminescence immunoassay with Elecsys1010 automatic analyzer (Roche Company). Inter-assay and intra-assay coefficient of variation were <4% and <7% respectively. The level of sensitivity is <1 pmol. LVEF was obtained by 2-dimensional echocardiography with HDI 3000 echocardiograph (ALT Company America).

Statistical Analysis

Data were expressed as mean±SD. Patients were divided into 3 groups according to their NYHA functional classification. Analysis of variance test was used to compare the difference of the levels of hsCRP and TNT among these 3 groups and the 25 control subjects. The correlation between the levels of hsCRP and TNT, hsCRP and LVEF were assessed by using Linear regression analysis. Cox proportional hazards analysis was performed to determine the significance of age, sex, LVEF, presence of ischemic heart disease, the use of statin drugs, and circulating levels of hsCRP as independent predictors of CHF. Patients were divided in 2 groups, patients who had major adverse cardiac events and those who were event-free. T-test for measurement data and chi-square test for enumeration data were performed to compare clinical and hemodynamic characteristics in these 2 groups.

Results

Circulating levels of hsCRP and TNT were significantly higher (3.85±4.25 mg/L, 0.21±0.15 mg/L, respectively) in patients with CHF than in 25 healthy people ($p<0.01$, $p<0.01$, respectively) and increased with severity of CHF. These data were shown in Table 2. Patients with CHF were divided in 2 groups according to the causes of their CHF (ischemic vs non-ischemic), serum levels of hsCRP had no significant difference between the 2 groups (4.13±5.12mg/L vs 4.09±5.24 mg/L, $p>0.05$).

During a mean follow up period of 378±26 days, forty-two (32.8%) of the 128 patients had cardiac events. Patients with CHF were divided into 2 groups, patients with cardiac events and those who were event free. There were no significant differences in age, sex, causes of CHF, or medications between the 2 groups. However levels of hsCRP and TNT were significantly higher ($p<0.001$, $p<0.001$, respectively) and LVEF was significantly lower ($p<0.01$) in patients with cardiac events than in patients without cardiac events. This data was shown in Table 3.

When multivariate Cox proportional hazards analysis was performed, we could find that hsCRP, TNT, and LVEF were independent significant predictors of cardiac events in patients with CHF. (hsCRP: hazard ratio [HR], 3.81; 95%CI, 2.14-9.35; P=0.024; TNT: HR, 2.61; 95%CI, 1.96-4.31; P=0.012; LVEF: HR, 3.52; 95%Cl, 2.36-10.37; P=0.024). A positive correlation was observed between hsCRP and TNT (r=0.493, $p<0.01$). A negative correlation was observed between hsCRP and LVEF (r=-0.354, $p<0.01$).

Table 2. The concentrations of hsCRP, TNT in patients with CHF and contral subjects

	Control	Class II	Class III	Class IV	*P*
hsCRP (mg/L)	1.01±0.54	2.64±3.12	4.51±5.21	6.34±7.36	<0.01
TNT (mg/L)	0.003±0.001	0.143±0.15	0.215±0.17	0.45±0.19	<0.05

Table 3. Characteristics of patients who had cardiac events and those who were event free

	Cardiac events (n=42)	Event free (n=86)	*P*
Age (y)	59±8	62±9	NS
Male (%)	26 (62%)	53 (62%)	NS
Causes of CHF			
Ischemic	24	51	NS
Non-ischemic	18	35	NS
Medications			
Diuretic	39	84	NS
Digitalis	34	70	NS
β-blockers	22	43	NS
ACEI/ARB	32	68	NS
Statins	10	21	NS
LVEF	0.22±0.14	0.36±0.15	*P<0.01*
hsCRP (mg/L)	6.59±7.69	2.46±3.25	*P<0.001*
TNT (mg/L)	0.48±0.11	0.11±0.02	*P<0.001*

NS: non significance

Discussion

CHF is the final common pathway of a variety of cardiac disorder, including ischemic heart disease, idiopathic dilated cardiomyopathy, and valvular disease, and is usually progressive. Recent studies suggest that heart failure may, in part, be an inflammatory disease.[2-4] CRP, an acute phase reactive protein that increases during the host response to tissue injury, including that caused by infection, trauma, malignant disease and chronic inflammatory conditions,[5] is synthesized in the liver, and its serum concentration is a reliable index of overall inflammation activity. Several large-scale prospective epidemiological studies have shown that plasma levels of hsCRP are a strong independent predictor of risk of future myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals without known cardiovascular disease.[6-10] Several studies have shown increased concentration of CRP in patients with heart failure,[11-15] but clinical data about the prognostic value of CRP in patients with chronic heart failure have been sparse and inconsistent.[11,12,16] Because standard assays for CRP lack the sensitivity needed to determine levels of inflammation within low reference range, and thus clinical utility of standard CRP is extremely limited to its prognostic values in patients with CHF. More recently, with the recognition that inflammation is one of the mechanisms of CHF and with the availability of highly sensitive assay systems, we thought that circulating concentrations of hsCRP may have prognostic value in patients with CHF.

Our study demonstrated that serum hsCRP concentration were elevated in patients with CHF and increased with severity of CHF. Furthermore, this study had shown that elevated serum hsCRP concentrations have independent significant predictive value. In our study we also found that hsCRP had a positive correlation with TNT and had a negative correlation with LVEF. The clinical and basic studies had shown that CRP has a fundamental role in atherogenesis.[17] Coronary artery disease was present in 68% of patients with CHF,[18] which cause, in part, elevated serum hsCRP in patients with CHF. This study also shown that increased hsCRP levels in patients with CHF was unrelated to the causes of heart failure, which suggests that CHF is the final common pathway of a variety of cardiac disorders, including ischemic heart disease, idiopathic dilated cardiomyopathy, and valvular heart disease.

Previous studies observed elevated serum levels

of TNT in patients with CHF,[19-21] and their presence was associated with adverse outcome.[17] Our results are consistent with the emerging concept that cardiac troponin elevations reflect ongoing myocardial cell injury associated with the progression of CHF. Also, the present study showed a positive correlation between TNT and hsCRP, speculating that markers specific for myocardial cell injury or inflammatory effect may detect different features of the pathophysiologic process of heart failure.

The mechanisms underlying the pathogenesis and progression of CHF remain unclear. Different mechanisms may be involved, such as activations of sympathetic nerve and renin-angiotensin-aldosterone systems. Both experimental and clinical studies have also shown a role for inflammation in the pathogenesis of heart failure. There is evidence that chronic activation of the immune system exists during heart failure. Some patients present evidence of monocyte-macrophage and lymphocyte activation.[22-25] It appears clear that patients with either ischemic or non-ischemic heart failure show activation of proinflammatory cytokines (IL-1, IL-6, tumor necrosis factor-α). Interleukin-6 is a major inducer of CRP.[26] Cardiac decompensation itself and injuries to other organs such as the liver, kidney, brain, or skeletal muscle induced by low cardiac output, hypoperfusion, hypoxia, and venous congestion may each be sources of interleukin-6, which may in turn result in the production of CRP in patients with CHF.[27] CRP has many pathophysiologic roles in the inflammatory process.[28] It can amplify the inflammatory response through complement activation, which may cause myocardial cell apoptosis, and thus ventricular damage or dysfunction.[29] This may resulted in mildly elevated levels of serum TNT in patients with CHF. In our study we found that hsCRP had a negative correlation with LVEF, this indicated a correlation between hsCRP and myocardial cell damage.

Whether CRP is simply a marker of chronic systemic inflammation or directly involved in the pathogenesis of CHF? Whether it can be used as a target for treatment of CHF? Further studies will be needed to answer this question.

In conclusion, serum hsCRP concentrations were elevated in patients with CHF and increased with severity of CHF. It was an independent significant predictor of cardiac events in patients with CHF.

References

1. Guidelines for the diagnosis of heart failure. The Task Force on Heart Failure of the European Society of Cardiology. Eur Heart J 1995;16:741-51.
2. Seta Y, Shan K, Bozkurt B, et al. Basic mechanisms in heart failure: the cytokine hypothesis. J Card Fail 1996;2:243-9.
3. Mann DL. Mechanisms and models in heart failure: A combinatorial approach. Circulation 1999;100:999-1008.
4. Sharma R, Coats AJ, Anker SD. The role of inflammatory mediators in chronic heart failure: cytokines, nitric oxide, and endothelin-1. Int J Cardiol 2000;72:175-86.
5. Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. Clin Chem 2003;49: 1258-71.
6. Koenig W, Sund M, Frohlich M, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999;99:237-42.
7. Roivainen M, Viik-Kajander M, Palosuo T, et al. Infections, inflammation, and the risk of coronary heart disease. Circulation 2000;101:252-7.
8. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506-12.
9. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321:199-204.
10. Mendall MA, Strachan DP, Butland BK, et al. C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. Eur Heart J 2000;21:1584-90.
11. Pye M, Rae AP, Cobbe SM. Study of serum C-reactive protein concentration in cardiac failure. Br Heart J 1990;63:228-30.
12. Kaneko K, Kanda T, Yamauchi Y, et al. C-Reactive protein in dilated cardiomyopathy. Cardiology 1999;91:215-9.
13. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M, et al. C-reactive protein as a predictor of improvement and readmission in heart failure. Eur J Heart Fail 2002;4:331-6.
14. Gottdiener JS, Arnold AM, Aurigemma GP, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2000;35:1628-37.
15. Sato Y, Takatsu Y, Kataoka K, et al. Serial circulating concentrations of C-reactive protein, interleukin (IL)-4, and IL-6 in patients with acute left heart decompensation. Clin Cardiol 1999;22:811-3.
16. Steele IC, Nugent AM, Maguire S, et al. Cytokine profile in chronic cardiac failure. Eur J Clin Invest 1996;26:1018-22.
17. Setsuta K, Ohtsuka T, Ogawa T, et al. Prognostic value of second generation cardiac troponin T in patients with chronic

heart failure. J Am Coll Cardio 1998;31:249A.
18. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998;97:282-9.
19. Missov E, Mair J. A novel biochemical approach to congestive heart failure: cardiac troponin T. Am Heart J 1999;138(1 Pt 1):95-9.
20. Setsuta K, Seino Y, Takahashi N, et al. Clinical significance of elevated levels of cardiac troponin T in patients with chronic heart failure. Am J Cardiol 1999;84:608-11, A9.
21. Xue C, Yu H, Li R, et al. Clinical significance of serum cardiac troponin T in patients with congestive heart failure. Chin Med J (Engl) 2003;116:469-71.
22. Werdan K. The activated immune system in congestive heart failure--from dropsy to the cytokine paradigm. J Intern Med 1998;243:87-92.
23. Samsonov M, Lopatin J, Tilz GP, et al. The activated immune system and the renin-angiotensin-aldosterone system in congestive heart failure. J Intern Med 1998;243:93-8.
24. Ferrari R, Bachetti T, Confortini R, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. Circulation 1995;92:1479-86.
25. MacGowan GA, Mann DL, Kormos RL, et al. Circulating interleukin-6 in severe heart failure. Am J Cardiol 1997;79: 1128-31.
26. Sato Y, Takatsu Y, Kataoka K, et al. Serial circulating concentrations of C-reactive protein, interleukin (IL)-4, and IL-6 in patients with acute left heart decompensation. Clin Cardiol 1999;22:811-3.
27. Yin WH, Chen JW, Jen HL, et al. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. Am Heart J 2004;147:931-8.
28. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-54.
29. Clark DJ, Cleman MW, Pfau SE, et al. Serum complement activation in congestive heart failure. Am Heart J 2001;141: 684-90.