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RESEARCH ARTICLE

Serum procollagen type III is associated with elevated right-sided filling pressures in stable outpatients with congestive heart failure

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Abstract

Elevated filling pressures are associated with heart failure deterioration, but mechanisms underlying this association remain poorly understood. We sought to investigate whether or not elevated filling pressures are associated with increased collagen turnover, evaluated by procollagen type III aminoterminal peptide (PIIINP) levels, in stable systolic heart failure. Eighty patients with heart failure with severe systolic dysfunction (ejection fraction 26 ± 7%) were included. Patients underwent simultaneous echocardiogram with evaluation of haemodynamic parameters and blood sampling for PIIINP measurement. Mean PIIINP level was 6.11 ± 2.62 μg l^{-1}. PIIINP was positively associated with estimated right atrial pressure (RAP) ($r = 0.36$; $p = 0.001$). Mean PIIINP values were 5.04 ± 2.42 μg l^{-1} in patients with estimated RAP ≤ 5 mmHg, and 7.59 ± 2.54 μg l^{-1} in those with RAP > 15 mmHg ($p < 0.01$). In conclusion, elevated right-side filling pressures are associated with evidence of active extracellular matrix turnover, as indicated by elevated PIIINP levels, in stable systolic heart failure. Activation of extracellular matrix turnover may be implicated in the accelerated progression of heart failure syndromes seen in patients with persistent congestion.

Keywords: *Congestive heart failure; haemodynamics; filling pressures; procollagen type III; remodelling*

Introduction

Left ventricular remodelling dominates progression of the heart failure syndrome. Accordingly, management of heart failure improved greatly once basic neurohormonal mechanisms involved in cardiac remodelling were understood and deemed to target therapies (Stevenson et al. 1995, Remme et al. 2004). Haemodynamic forces are also important in inducing changes in ventricular function and structure. It is known that elevated filling pressures and increased afterload are deleterious to the maintenance of cardiac stroke volume in advanced stages of heart failure (Stevenson & Tillisch 1986). In accordance with these observations, we and others have shown that patients maintaining signs and symptoms of congestion and with echocardiographic-derived parameters indicating elevated filling pressures have higher rates of clinical events, including heart failure-related decompensation episodes (Stevenson et al. 1990, Rohde et al. 2004).

The extracellular matrix (ECM) plays an active role in myocardial remodelling. Fibrillar collagen types I and III are main components of ECM and important determinants of the structural and functional integrity of the myocardium (Weber et al. 1994, Brower et al. 2006). Increased deposition of collagen and alterations in relative abundance of type I and III collagens are described in the failing myocardium and are thought to have deleterious effects in cardiac geometry and function (Brower et al. 2006). Increased serum levels of procollagen type III N-terminal peptide (PIIINP), a marker of type III collagen turnover, have been shown in patients with systolic heart failure, indicating a worse prognosis (Cicoira et al. 2004). Furthermore, PIIINP levels are associated

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with myocardial collagen deposition (Klappacher et al. 1995), and to post-myocardial infarction remodelling (Poulsen et al. 2000). PIIINP levels are therefore related to pathological ECM turnover and myocardial remodelling in patients with heart failure.

Increased wall stress seems to stimulate excessive collagen turnover through the activation of matrix metalloproteinases (Li et al. 2001, Spinale 2007). Therefore, increased collagen turnover could be involved in the observed relationship between haemodynamic profile and adverse cardiac remodelling in patients with heart failure. However, there is no direct information on whether ECM turnover is correlated with elevated filling pressures in patients with stable compensated heart failure. We therefore sought to investigate whether or not elevated ECM turnover as reflected by circulating levels of PIIINP correlates with findings suggestive of elevated filling pressures in stable outpatients with systolic heart failure.

Methods

We studied patients with a heart failure diagnosis of more than 6 months followed at out Heart Failure clinic, regardless of aetiology, with echocardiography-based left ventricular ejection fraction equal or less than 40%, who were in a stable condition. Clinical stability was defined as no emergency visits or hospital admissions for acute decompensation of HF in the 3 months prior to study entry. At enrolment, study subjects had peripheral venous blood samples collected to perform routine biochemical tests and PIIINP measurements, which were performed using a commercially available radioimmunoassay kit (Orion Diagnostica, Espoo, Finland). The sensitivity (lowest detection limit) was 0.2 ng ml^{-1}. Inter- and intra-assay variations ranged from 3% to 10%. All blood samples were obtained simultaneously with echocardiographic examinations.

M-mode and two-dimensional colour Doppler echocardiography was performed by an experienced cardiologist using commercially available ultrasound equipments (ATL HDI 5000; Advanced Technology Laboratories, Bothel, WA, USA). Echocardiographic parameters were evaluated according to standard recommendations of the American Society of Echocardiography (Schiller 1991). Haemodynamic parameters were determined according to previously validated protocols (Stein et al. 1997, Rohde et al. 2007). For each measurement, three to five consecutive cardiac cycles were measured and averaged. In brief, pulmonary artery systolic pressure was estimated as the sum of the estimated right atrial pressure (RAP) and the pressure gradient between the right ventricle and right atria. RAP was estimated by measuring the inferior vena cava diameter and its degree of collapsibility during inspiration (Kircher et al. 1990). Cardiac output was determined by multiplying heart rate by stroke volume. Left ventricular systolic volume was estimated by multiplying the time-velocity integral of the left ventricular outflow by the estimated left ventricular outflow area. Systemic vascular resistance was calculated using standard haemodynamic formulas, incorporating cardiac output and mean arterial pressure estimations. Systemic vascular resistance and cardiac output were indexed by body surface area. Intraobserver variability for echocardiography-based haemodynamic calculations in our non-invasive laboratory is excellent ($r = 0.95$, $p < 0.001$ for cardiac output and $r = 0.99$, $p < 0.001$ for pulmonary artery systolic pressure) (Rohde et al. 2007)

The study was conducted according to the Declaration of Helsinki, and the research protocol was approved by the Ethics and Research Committee of the institution. All patients gave their written informed consent prior to study enrolment. All analysed variables demonstrated a normal distribution. Student's *t*-test was used to compare levels of PIIINP according to use or not of heart failure medications. Correlation coefficients among PIIINP levels and left ventricle function/structure and filling pressures were obtained using Pearson's correlation test. One-way ANOVA followed by Tukey with *post-hoc* correction was used to evaluate further if PIIINP values were associated with different categories of RAP (≤ 5 mmHg, 6–15 mmHg and > 15 mmHg) (Lee et al. 2007). Finally, a receiver operator curve analysis was performed to determine the ability of PIIINP to discriminate patients in the highest RAP group. A two-sided *p*-value of less than 0.05 was considered statistically significant. Data were analysed using the SPSS 12.0 software program for Windows (SPSS Inc., Chicago, IL, USA).

Results

Eighty patients with heart failure constituted the study population. The mean age was 59 ± 15 years and ejection fraction was 26 ± 7%. Overall, 61.5% of patients were male and 25% presented CHF of ischaemic aetiology. Echocardiographic-derived haemodynamic data demonstrated that the studied patients presented elevated right- and left-sided filling pressures, low cardiac output and increased systemic vascular resistance (Table 1). Almost all enrolled subjects were using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and most of them were on beta-blockers and spironolactone.

Mean PIIINP levels did not vary according to different heart failure aetiologies (6.31 ± 2.53 μg l^{-1} for ischaemic vs 6.04 ± 2.66 μg l^{-1} for non-ischaemic, $p = 0.7$). Similarly, PIIINP values did not differ between patients taking or not taking usual heart failure medications such as beta-blockers or spironolactone. In particular, values of PIIINP in patients using beta-blockers were 6.02 ± 2.61 μg l^{-1} compared with 6.2 ± 2.65 μg l^{-1} in non-beta-blockers users ($p = 0.7$). There was a trend for increased PIIINP levels with higher functional classes ($P = 0.08$ for trend across functional classes I to IV).

PIIINP levels were significantly higher in patients with elevated RAP (7.59 ± 2.54 μg l^{-1} in patients with RAP > 15 mmHg) compared with those with RAP ≤ 5 mmHg (5.04 ± 2.42 μg l^{-1}) (Figure 1) and showed a positive correlation with RAP ($r = 0.36$; $p = 0.001$, Figure 2). We further evaluated the ability of PIIINP values to discriminate patients with RAP > 15 mmHg, and the area under the receiver operator curve was 0.72 (0.60–0.84, $p = 0.003$).

Correlations between PIIINP and other echocardiographic parameters of left ventricular function and haemodynamic estimates were also performed. However, none of them were linearly associated with PIIINP levels (left ventricular ejection fraction, $r = 0.1$ and $p = 0.4$; cardiac index, $r = -0.15$ and $p = 0.18$; systemic vascular resistance index, $r = 0.06$ and $p = 0.6$).

Table 1. Clinical characteristics and haemodynamic profile of study patients according to right atrial pressure (RAP) levels.

	RAP categories (mmHg)				
	All patients($n = 80$)	≤5($n = 15$)	6–15($n = 46$)	>15($n = 19$)	*p*-Value
Age (years)	59 ± 15	62 ± 14	59 ± 16	59 ± 13	0.7
Sex, male	49 (61.5)	11 (73.5)	27 (58.5)	11 (58)	0.5
Functional class I–II, SAS	56 (70)	10 (66.5)	36 (78)	10 (52.5)	0.1
Aetiology, ischaemic	20 (25)	2 (13.5)	14 (30.5)	4 (21)	0.4
LV ejection fraction (%)	26 ± 7	31 ± 5	25 ± 7	24 ± 8	0.03
LV end-diastolic diameter (mm)	67 ± 8	61 ± 8	68 ± 7	70 ± 7	0.002
SBP (mmHg)	120 ± 20	128 ± 21	118 ± 20	117 ± 16	0.2
Heart rate (bpm)	85 ± 19	88 ± 20	82 ± 18	87 ± 17	0.4
Cardiac index (l min^{-1} m^{-2})	1.8 ± 0.5	1.9 ± 0.5	1.8 ± 0.5	1.6 ± 0.6	0.3
SVRI (dyn s m^2cm^{-5})	3852 ± 1196	3854 ± 1322	3772 ± 1147	4042 ± 1253	0.7
Creatinine (mg dl^{-1})	1.1 ± 0.3	1.1 ± 0.4	1.0 ± 0.2	1.1 ± 0.3	0.3
Sodium (mEq l^{-1})	137 ± 3	137 ± 3	136 ± 3	137 ± 4	0.7
ACE inhibitors or ARB	79 (99)	15 (100)	46 (100)	18 (94.5)	0.2
Beta-blockers	42 (52.5)	8 (53.5)	28 (61)	6 (31.5)	0.09
Spironolactone	42 (52.5)	9 (60)	24 (52.5)	9 (47.5)	0.7
PIIINP (μg l^{-1})	6.02 ± 2.63	5.04 ± 2.42	5.84 ± 2.46	7.59 ± 2.63	0.009

Data are expressed as mean ± SD or number (%). SAS, Specific Activity Scale; LV, left ventricle; SBP, systolic blood pressure; SVRI, systemic vascular resistance index; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; PIIINP, pro-collagen type III.

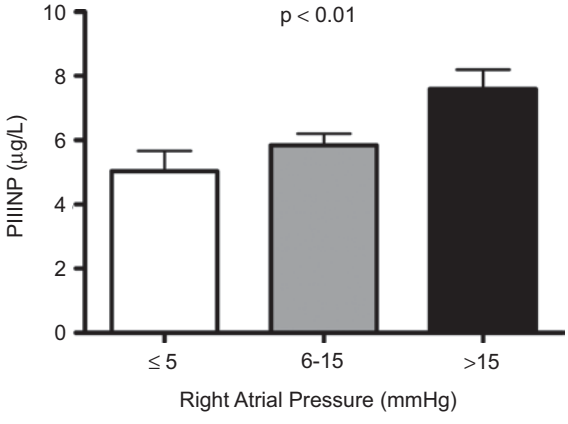

Figure 1. Procollagen type III aminoterminal peptide (PIIINP) values (mean ± SEM) among right atrial pressure (RAP) categories; $p < 0.01$ for one-way ANOVA among groups. *$p < 0.05$ for Tukey *post-hoc* for RAP > 15 mmHg vs 6–15 mmHg and ≤ 5 mmHg groups.

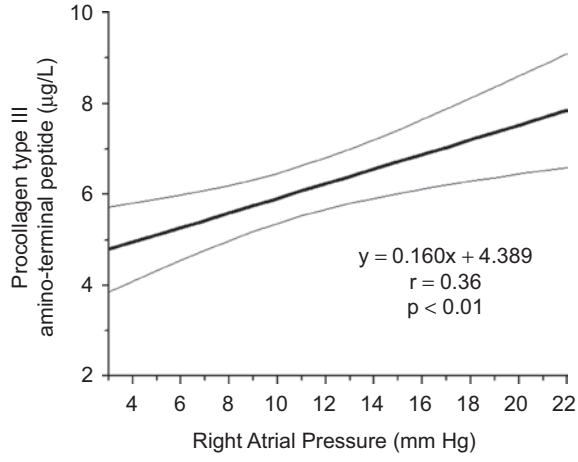

Figure 2. Graph illustrating the correlation between right atrial pressure and levels of procollagen type III aminoterminal peptide (PIIINP).

Discussion

Patients with signs, symptoms and haemodynamic profile indicating congestion have poorer prognosis in the heart failure setting (Stevenson et al. 1990, Lucas et al. 2000, Rohde et al. 2004, Rohde et al. 2007). In this study, we showed that elevated levels of PIIINP in outpatients with heart failure correlated with elevated right-side filling pressures assessed non-invasively by echocardiography. These findings suggest that increased extracellular matrix turnover may underlie progressive myocardial remodelling in the context of elevated filling pressures.

Stevenson and colleagues suggested that a more aggressive approach for congestion aiming at near-normal filling pressures is beneficial in advanced heart failure (Stevenson & Tillisch 1986, Stevenson et al. 1990). In the current investigation, we found that echocardiographic-derived haemodynamic parameters showed a wide range of intracardiac filling pressures as expressed by RAP values in patients with stable heart failure. In fact, in our patients, despite some features indicating less advanced disease (functional class I or II in most patients and relatively normal systolic blood pressure), clearly elevated right-side filling pressures were present in the majority of subjects. This finding in itself underscores the challenge for clinicians to define accurately volume status in the outpatient setting and to implement appropriate therapy. Accordingly, we have also recently shown that aiming for a near-normal echocardiographic-derived haemodynamic profile, based on echocardiographic values rather than clinical exam alone was associated with improvement in clinical endpoints in stable outpatients with heart failure (Rohde et al. 2007). Taken together, these findings suggest that aiming at lowering filling pressures could be beneficial in both the advanced and stable outpatient heart failure scenario. However, the mechanisms related to improved prognosis once patients are maintained in a dry profile are not completely understood. The present study raises potential pathophysiological hypotheses that may be involved in these previously reported findings. The main finding of our study is that patients with elevated RAP do have evidence of active ECM turnover as expressed by elevated levels of PIIINP.

Interestingly, in addition to neurohormonal influences, the excessive or altered production of ECM collagen involved in myocardial remodelling is thought to be regulated to some extent by mechanical and haemodynamic factors (Li et al. 2001). As compensatory mechanisms become maladaptive, increased wall stress, resulting from elevated ventricular filling pressures and elevated left ventricle afterload, has been shown to stimulate adversely excessive ECM collagen turnover in experimental models (Rohde et al. 1999), possibly contributing to the progression of myocardial dysfunction and adverse prognosis in heart failure (Spinale 2007).

In conclusion, this study demonstrated that elevated right-sided filling pressures are associated with evidence of active ECM turnover, as indicated by elevated PIIINP circulating levels, in stable systolic heart failure outpatients. These findings suggest that activation of ECM turnover and fibrosis may be implicated in the accelerated progression of heart failure syndromes seen in patients with persistent congestion.

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