SCIENTIFIC LETTERS

Reduction in Fas/APO-1 plasma concentrations correlates with improvement in left ventricular function in patients with idiopathic dilated cardiomyopathy treated with pentoxifylline

Inflammatory cytokines have been related to the pathogenesis and progression of heart failure.¹ Cytokines can modulate cardiovascular function through different mechanisms, such as depressing contractile function, promoting left ventricular remodelling, uncoupling myocardial β adrenergic receptors, and inducing apoptosis. Loss of myocytes caused by apoptosis or programmed cell death occurs in patients with heart failure and may contribute to progressive myocardial dysfunction.² Fas is an apoptosis signalling surface receptor known to trigger programmed cell death in a variety of cell types,³ and increased plasma concentrations of soluble Fas receptors have been reported in patients with heart failure. Pentoxifylline is a xanthine derived agent known to inhibit the production of tumour necrosis factor α (TNF α). It was also found to inhibit apoptosis in different human cell types in vitro and in vivo.⁴ However, the effects of pentoxifylline on apoptosis signalling receptors in patients with heart failure has not been investigated. We have previously reported beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy.⁵ Treatment with pentoxifylline resulted in a significant improvement in functional class and left ventricular function, and was associated with a reduction in TNF α plasma concentrations. The aims of the present study were to evaluate: (1) the effects of pentoxifylline on Fas/APO-1 plasma concentrations in patients with idiopathic dilated cardiomyopathy; (2) the possible correlation between the changes in the cytokine or Fas concentrations and the changes in left ventricular ejection fraction following six months of treatment with pentoxifylline; and (3) to establish predictors of outcome.

In a single centre, prospective, double blind, randomised, placebo controlled trial, we included 49 patients with idiopathic dilated cardiomyopathy in New York Heart Association functional class II or III and left ventricular ejection fraction <40% by radionuclide angiography. All patients received treatment with digoxin, diuretics, and angiotensin converting enzyme inhibitors. After baseline examinations were performed, patients were randomised to pentoxifylline 400 mg three times daily ($n = 25$) or a matching placebo ($n = 24$). Mean (SD) age of the study population was 52 (11) years and baseline mean left ventricular ejection fraction 23 (9)%. There were no significant baseline differences between groups. Eight patients died during the study period (six in the placebo group). Treatment with pentoxifylline was associated with a significant improvement in functional class, and left ventricular ejection fraction (21 (8)% to 35 (16)%, $p = 0.0007$). No significant changes in left ventricular dimensions or function

were observed in the placebo group. Twelve of the patients treated with pentoxifylline showed an improvement of the ejection fraction > 10 absolute units, and were arbitrarily defined as improvers, whereas only two patients in the placebo group showed a similar degree of improvement ($p = 0.008$ between groups).

TNF α and Fas plasma concentrations were significantly higher in the study group compared to 20 healthy volunteers (7.4 (5) pg/ml *v* 1.4 (1) pg/ml, $p < 0.0001$; and 6.7 (5) U/ml *v* 0.8 (0.2) U/ml, $p < 0.0001$, respectively). Baseline concentrations of TNF α and Fas were similar in the placebo and treatment arms. Patients treated with pentoxifylline had a significant reduction in the TNF α (6.6 (5) pg/ml to 1.9 (1) pg/ml, $p = 0.0005$) and Fas plasma concentrations (8.0 (7) U/ml to 5.5 (6) U/ml, $p = 0.004$) after six months, with no significant changes in the placebo group.

Despite a similar ejection fraction at baseline, non-improvers had larger left ventricular end diastolic ($p = 0.06$) and end systolic diameters ($p = 0.05$), and a higher E/A ratio ($p = 0.03$) compared to improvers. Baseline TNF α plasma concentration was significantly higher in the 12 patients that were defined as improvers in the pentoxifylline group compared to non-improvers (7.26 (3.2) pg/ml *v* 3.66 (2.3) pg/ml respectively, $p = 0.01$). Similarly, there was also a trend towards higher baseline Fas concentrations among improvers ($p = 0.09$). No other significant differences in the baseline characteristics were noted between these two groups. Following six months of treatment with pentoxifylline, both improvers and non-improvers showed a significant reduction in TNF α concentrations, although there was a trend towards a more significant decline among the improvers (reduction of 5.2 (4) pg/ml *v* 2.0 (3) pg/ml in improvers and non-improvers respectively, $p = 0.06$). There was a significant correlation between baseline Fas/APO-1 plasma concentrations, and changes in ejection fraction after treatment ($r = 0.47$, $p = 0.03$), and a significant negative correlation between the changes in Fas plasma concentrations, and the changes in ejection fraction at six months ($r = -0.49$, $p = 0.03$). No significant correlation was observed between baseline TNF α concentrations or changes in TNF α concentration, and changes in ejection fraction following treatment. Of all baseline variables analysed, only Fas/APO-1 concentration and E/A ratio emerged as independent predictors of improvement in the multivariate analysis ($p = 0.02$).

The reduction in Fas concentrations observed in this study suggests a possible inhibition of apoptosis by pentoxifylline. The finding that baseline concentrations of TNF α and Fas/APO-1 concentrations were higher in patients with a more favourable response to treatment is important to help us to understand the mechanism of action of pentoxifylline in patients with heart failure. The lack of statistical correlation between the changes in cytokine concentrations and the changes in left ventricular function might be explained by the fact that in the pentoxifylline group TNF α dropped even in patients that did not improve the ejection fraction. Finally, although current evidence supports the proposal that apoptosis occurs in heart failure, it is still unclear to what extent it contributes to the progression of myocardial dysfunction. Hirota and colleagues,⁶ using a gene

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knockout mice model, recently showed that apoptosis plays a critical role in the transition between compensatory cardiac hypertrophy and heart failure during aortic pressure overload. Therefore, the use of treatments that can block apoptotic pathways could be a useful strategy in the treatment of patients with heart failure. The results of our study suggest that attenuation of apoptosis together with a reduction in TNF α concentrations may be

the mechanism of improvement of left ventricular function in patients with idiopathic dilated cardiomyopathy treated with pentoxifylline.

D SKUDICKY
K SLIWA
A BERGEMANN
G CANDY
P SARELI

Department of Cardiology,
Baragwanath Hospital,
University of the Witwatersrand,
Johannesburg, South Africa
dskudi@icon.co.za

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Increased formation of F₂-isoprostanes in patients with severe heart failure

During the last decade, considerable interest has been focused on the potential role of oxygen free radical generation in the pathophysiology of chronic congestive heart failure. Oxidative stress has been demonstrated in different animal models of congestive heart failure: volume overload, pressure overload, myocardial infarction, and adriamycin-induced cardiomyopathy. In contrast with animal studies, human studies are less convincing given that most of the traditional methods used to assess oxidative stress in the clinical setting are non-specific or inaccurate.¹

A novel family of prostaglandin F₂ isomers, called F₂-isoprostanes, produced in vivo by a free radical peroxidation of arachidonic acid,

has recently been described.² Isoprostaglandin F_{2α} type III, formerly known as 8-isoprostaglandin F_{2α}, is a biochemically stable F₂-isoprostane, formed by direct free radical peroxidation of arachidonic acid of cell membranes or circulating low density lipoprotein.² Its quantification in tissues and biological fluids has been suggested to be a reliable measure of oxidant injury in vivo. Indeed, urinary excretion of this compound has been well characterised and is currently used as an index of lipid peroxidation in human diseases. A recent study has shown that concentrations of isoprostaglandin F_{2α} type III were increased in pericardial fluid of patients with symptomatic heart failure.³ However, urinary measurements may be of more clinical use for follow up studies. The purpose of the present study was to investigate urinary isoprostaglandin F_{2α} type III formation as an index of lipid peroxidation in patients suffering from severe heart failure.

Twenty five consecutive patients suffering from heart failure were included between April and July 1999. Patients were referred before heart transplantation or for a left ventricular failure episode. Patients were matched with 25 healthy volunteers (22 men, 3 women, median age 56 years (range 25-73 years), 11 smokers). The criterion for admission into the study was a left ventricular ejection fraction < 45%. Criteria for exclusion were severe valve disease and congenital heart disease. Two subgroups of patients were identified: seven patients with chronic heart failure secondary to ischaemic heart disease—that is, documented myocardial infarction and/or angiographically demonstrated coronary artery disease; and 18 patients with idiopathic dilated cardiomyopathy, with angiographically normal coronary arteries. The clinical characteristics of the patients are depicted in table 1.

This study conformed to the principles outlined in the declaration of Helsinki.

Complete M mode (one dimensional) and cross sectional (two dimensional) echocardiographic examinations were performed in all patients. Left ventricular end diastolic and end systolic volumes were measured from the parasternal long and short axis views, and the ejection fraction calculated. Exercise tests were performed two months after the last

Figure 1 Urinary concentration of isoprostaglandin F_{2α} type III in controls (n = 25), and patients in NYHA classes II (n = 10), III (n = 9), and IV (n = 6). The line drawn through the middle of the boxes represents the median. The top and bottom of the boxes are the 75th and 25th centiles. The top and bottom of the T bars are the 90th and 10th centiles.

*p < 0.05 versus class II and III.

episode of acute left ventricular failure in 14 patients. Oxygen consumption (Vo₂) was determined during the stress test by a cycle to cycle method (Medical Graphics). Vo₂ measurements were expressed as a percentage of the predicted normal values for sedentary adults (Vo₂max).

Urine samples were collected during hospitalisation between 8 and 10 am in polyethylene tubes (20 ml), after which they were transferred to the laboratory, aliquoted, and stored at -20°C. Samples were extracted using a method derived from that previously described by Nourooz-Zadeh.⁴ Isoprostaglandin F_{2α} type III (8-isoprostane F_{2α}) and 11-dehydro-thromboxane B₂ concentrations were determined by enzyme immunoassay (Cayman, Ann Arbor, USA). The results obtained in pg/ml were standardised versus urinary creatinine concentrations. Final results were expressed as pmol/mmol of creatinine.

Continuous variables were expressed as means with standard deviations in parentheses. Analysis of variance (Kruskal-Wallis method, followed by Mann-Whitney U test) was used for statistical comparisons. Regression analyses were performed using the Spearman rank correlation test. Values of p < 0.05 were considered significant.

Urinary excretion of isoprostaglandin F_{2α} type III was significantly higher (p < 0.0001) in patients suffering from severe heart failure compared with age and sex matched controls: 259 (191) versus 110 (36) pmol/mmol creatinine (fig 1). Concentrations of isoprostaglandin F_{2α} type III in New York Heart Association (NYHA) class IV patients were significantly higher (p < 0.05) than those in NYHA class II and III: 426 (296) versus 199 (83) and 214 (139) pmol/mmol, respectively (fig 1). Urinary excretion of 11-dehydro-thromboxane B₂ was significantly higher (p < 0.001) in patients compared with controls: 317 (242) versus 119 (64) pmol/mmol. However, no significant differences were found between the different functional classes.

Table 1 Clinical characteristics of 25 patients with severe heart failure

Age (years) (median, range)	57 (27-75)
Sex ratio men/women	22/3
Body mass index (kg/m ²)	24.6 (3)
Smokers	12/25
Disease duration (months) (median, range)	12 (0-96)
Aetiology of heart failure	
Ischaemic cardiomyopathy	28%
Idiopathic dilated cardiomyopathy	72%
NYHA functional class	
II	40%
III	36%
IV	24%
LVEF (%)	25 (11)
LVEDD (mm)	66.4 (8)
Vo ₂ max (% predicted values), n = 14	67 (18)
Medications	
ACE inhibitors	92%
Loop diuretics	88%
Digoxin	72%
Spironolactone	48%
β blockers (carvedilol)	40%
Aspirin	40%
Oral anticoagulant treatment	28%
Nitrates	4%

ACE, angiotensin converting enzyme; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; Vo₂ max, percentage of the predicted normal values for peak oxygen consumption during exercise testing. Data are presented as mean with standard deviation in parentheses, except for age and disease duration which are expressed as median with range in parentheses.

Urinary concentrations of isoprostaglandin $F_{2\alpha}$ type III were not correlated to left ventricular end diastolic diameter or to left ventricular ejection fraction. A difference between ischaemic and idiopathic dilated cardiomyopathy subgroups was not observed. There was a non-significant trend towards a correlation between isoprostaglandin $F_{2\alpha}$ type III concentrations and $VO_{2\max}$. A significant correlation was found between isoprostaglandin $F_{2\alpha}$ type III and 11-dehydro-thromboxane B_2 urinary concentrations ($r = 0.64$, $p < 0.001$), suggesting a link between lipid peroxidation and platelet activation.

No significant differences in isoprostaglandin $F_{2\alpha}$ type III urinary concentrations were found between patients on aspirin versus those not on aspirin (241 (118) v 271 (230) pmol/mmol respectively), or between patients on carvedilol versus those not on carvedilol (256 (140) v 260 (220) pmol/mmol, respectively).

In our study, a significant increase in isoprostaglandin $F_{2\alpha}$ type-III concentrations was found in the urine samples from patients with severe heart failure compared with controls, independent of cardiac failure aetiology. Consistent with a previous study on pericardial concentrations of isoprostaglandin $F_{2\alpha}$ type III,³ we found a correlation between the functional classes and the urinary concentration. Furthermore, there was a trend towards a correlation between isoprostaglandin $F_{2\alpha}$ type III concentrations and $VO_{2\max}$. These results suggest that oxidative stress is correlated with the progression of heart failure and with the deterioration of functional capacity. However, it remains undetermined whether lipid peroxidation plays a pathophysiological role in the evolution of cardiac failure, or if isoprostaglandin $F_{2\alpha}$ type III only reflects tissue damage in patients with heart failure. It has been suggested that free radical generation may play a role in both contractile dysfunction and structural damage to the myocardium. Furthermore, isoprostaglandin $F_{2\alpha}$ type III has been shown to be a potent vasoconstrictor in animal and human vascular beds. As a consequence, isoprostaglandin $F_{2\alpha}$ type III may contribute to the increased peripheral and pulmonary vascular tone observed in cardiac failure and thus contribute to the functional deterioration.

Urinary 11-dehydro-thromboxane B_2 —an index of thromboxane synthesis *in vivo*—was increased in heart failure patients, suggesting enhanced platelet activation. This finding is in accordance with those of a recent study, in which both soluble and platelet bound P-selecting concentrations were higher in patients with heart failure compared with controls.⁵ The correlation observed between 11-dehydro-thromboxane B_2 and isoprostaglandin $F_{2\alpha}$ type III excretion is consistent with a link between enhanced lipid peroxidation and platelet activation in heart failure.

An important advantage of isoprostaglandin $F_{2\alpha}$ type III measurement in urine over other methods is that it is non-invasive, reproducible, and may be repeated over time. Several therapeutic approaches including carvedilol, amiodarone, and vitamin E have recently been shown to protect cardiac myocytes against oxidative injury *in vitro*. The results of the present study provide a rationale for clinical trials based on measurements of F_2 -isoprostanes to assess the antioxidant properties of these drugs in heart failure. Indeed, such an approach has recently been described in hypercholesterolaemia and diabetes. In both studies, vitamin E

supplementation induced dose dependent reductions in F_2 -isoprostanes concentrations.

The present study shows that severe heart failure is associated with an increase in urine concentrations of isoprostaglandin $F_{2\alpha}$ type III, an index of lipid peroxidation. Urinary measurement of F_2 -isoprostanes may provide a non-invasive biochemical end point for antioxidant therapeutics investigations in heart failure.

J L CRACOWSKI

F TREMEL*

C MARPEAU

J P BAGUET*

F STANKE-LABESQUE

J M MALLION*

G BESSARD

Laboratory of Pharmacology,

LSCPA EA2937,

Faculté de Médecine de Grenoble,

F-38706 La Tronche Cedex, France

Internal Medicine and Cardiology Department,*

Hôpital Michallon CHU,

Grenoble BP 217,

38043 Grenoble Cedex 9, France

Jean-Luc.Cracowski@ujf-grenoble.fr

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Commentary

Isoprostaglandin $F_{2\alpha}$, also known as isoprostaglandin $F_{2\alpha}$ type III, is a member of a group of prostanoids called F_2 -isoprostanes. These are produced as a result of cell membrane lipid peroxidation mediated by reactive oxygen species (free radicals). This small study reports that urinary excretion of isoprostaglandin $F_{2\alpha}$ can be used to assess the extent of oxidative stress in heart failure patients and that urinary concentrations correlate with the functional severity of disease. The technique may have potential for development as a non-invasive quantitative tool for monitoring response to treatment in patients with heart failure.

G F BAXTER

Associate Editor

Failure of plasma brain natriuretic peptide to identify left ventricular systolic dysfunction in the community

Heart failure is a major public health problem. The clinical diagnosis is imprecise and a simple test of left ventricular function would greatly improve diagnostic accuracy. Measurement of brain natriuretic peptide (BNP) has been shown in some studies to be a potential marker of left ventricular dysfunction.¹ Heart failure is more common in the elderly and is often treated in the community where a simple test would be of considerable benefit. We have therefore measured plasma BNP values and compared

them with echocardiographic measures of left ventricular function in a large, community based population.

Eight general practices of a total list size of 65 820 were surveyed. All patients currently prescribed loop diuretics were invited to take part in the study as it was thought the majority of patients with the clinical syndrome of heart failure would be treated with them. Of the 1425 patients asked to participate, informed consent, echocardiograms, and measurement of plasma BNP were obtained in 653. The median age of the group was 76 years with an interquartile range (IQR) of 70-82 years. The group was composed of 254 males and 399 females. Patients took all usual medication and were not subjected to any dietary restrictions. The study was approved by the local committee on medical research ethics.

Left ventricular volumes were measured by two dimensional (cross sectional) echocardiography using a phased array sector scanner (Vingmed CFM 700). The images were analysed using a computer assisted, video overlay, echocardiographic analysis system (Thoraxcenter, Erasmus University, Rotterdam, The Netherlands). An apical four chamber view was used for imaging and a modified Simpson's single plane disc method for analysis. The method has been described previously.² All echocardiograms were performed by three experienced operators and all analyses by two technicians.

Venous blood for measurement of BNP was collected into chilled tubes containing 1 mg/ml EDTA and 1000 KIU/ml aprotinin. Plasma was separated within one hour and stored at -70°C until analysis. All samples were extracted within four weeks and assayed by radioimmunoassay.

Plasma samples were acidified and extracted using preactivated Sep Pak C18 cartridge (Waters Corporation, Milford, Massachusetts, USA). The eluates were dried under vacuum using a centrifugal evaporator and stored frozen until assayed. The precipitates were resuspended in assay buffer and assayed by radioimmunoassay (Peninsula Laboratories, St Helens, UK).

Extraction of plasma samples with known amounts of standard hBNP-32 added ($n = 12$) gave a mean (SD) recovery of 83 (12.5)%. The intra- and inter assay coefficients of variation for the assay were 5.6% ($n = 10$) and 9.6% ($n = 20$), respectively. All the samples for the study were extracted and assayed by either of two experienced operators, who were blinded to the echocardiograph data. Blood samples taken from 50 healthy subjects aged from 20 to 81 years with no evidence of cardiac disease gave a median plasma BNP of 33 pg/ml (22-40 pg/ml IQR).

There was a significant negative correlation between plasma BNP and left ventricular ejection fraction (fig 1A; $r = -0.1695$, $p < 0.001$ (Spearman correlation coefficient), $n = 653$). There was also a significant correlation between plasma BNP and both left ventricular end diastolic volume index ($r = 0.2640$, $p < 0.001$, $n = 652$) and left ventricular end systolic volume index ($r = 0.2710$, $p < 0.001$, $n = 652$).

In patients with a left ventricular ejection fraction above 40% the median (IQR) plasma BNP concentration was 47 pg/ml (32-79 pg/ml) compared to 60 pg/ml (38-97 pg/ml) in those with an LVEF of $< 40\%$ (Wilcoxon rank sum test; $p < 0.001$). The plasma BNP

Figure 1 (A) Brain natriuretic peptide (BNP) concentration against left ventricular ejection fraction (LVEF). (B) Graph showing distribution of plasma BNP concentrations when the cohort is divided using an ejection fraction of 40% as the cut off point. Solid bars indicate median values, dashed bars represent the lower and upper quartiles.

concentrations for both groups are presented as a scatterplot in fig 1B.

A receiver operator characteristic (ROC) curve was constructed (SAS statistical software) to assess the sensitivity and specificity of BNP to detect left ventricular systolic dysfunction. The area under the curve, which provides a measure of the overall diagnostic

accuracy of the test, was 0.587, indicating poor sensitivity and specificity.

This study has demonstrated a significant correlation between plasma BNP and echocardiographic measures of left ventricular systolic dysfunction. However, the correlation coefficient indicates the relation is not close and the area under the ROC curve was

much less than reported in other studies.^{3,4} This suggests that the accuracy of BNP concentrations to provide a measure of left ventricular function and help diagnose heart failure is not as good as previously reported. The reason for the differences between our results and those of others is not clear. We believe our BNP assay is robust and the echocardiograms were performed by a small number of experienced operators and analysed in a standardised way. It is possible that our patients were different to those included in other studies. We deliberately chose patients who general practitioners thought might have heart failure and had accordingly treated them with diuretics. The diagnostic difficulties are clearly more important in the community. Furthermore the age of the patients included in this study was much higher than in others, but also the prevalence of heart failure is much higher in the elderly. We do not believe the previous prescription of diuretics would have adversely affected our results, as there is no evidence diuretics change BNP concentrations or have significant effects on echocardiographic measures of ejection fraction. The results of this study suggest that BNP concentrations may not be as accurate an aid to the diagnosis of heart failure as previously stated.

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D J HETMANSKI
N J SPARROW*
S CURTIS
A J COWLEY

Cardiovascular Medicine and
Centre for Continuing Postgraduate Medical
Education*,
University Hospital,
Nottingham, UK
alan.cowley@nottingham.ac.uk

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