SCIENTIFIC LETTER

Transcardiac and transpulmonary gradients in the putative new cardiovascular hormone relaxin

C Fisher, S Al-Benna, A Kirk, J J Morton, J J V McMurray

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Relaxin, a polypeptide hormone belonging to the insulin family, has recently attracted interest as a possible cardiovascular regulator.¹ Though long known to prepare the birth canal for parturition, relaxin has only lately been shown to have renal and haemodynamic actions.² Relaxin may also be secreted by the heart, at least when it is failing.³ Plasma relaxin concentrations are raised in chronic heart failure (CHF) and myocardial expression of the H1 and H2 relaxin gene is increased in proportion to the severity of CHF. Whether the heart is a source of relaxin when cardiac contractility is preserved is unknown. The lungs are commonly involved in the clearance or secretion of vasoactive peptides but their role in relaxin metabolism is unknown.⁴ The aim of this study was to measure transcardiac and transpulmonary relaxin gradients in subjects with preserved left ventricular ejection fraction. Patients undergoing coronary artery bypass grafting were studied as both pulmonary and cardiac arterial inflow and venous effluent can be readily sampled.

METHODS

Twenty consecutive patients were studied. Immediately before institution of cardiopulmonary bypass, blood samples were taken into chilled tubes, in rapid succession, from the aorta, coronary sinus, pulmonary artery, and pulmonary vein.⁴ A validated relaxin immunoassay was used (Immundiagnostik, Bensheim, Germany).³ Statistical analysis was performed using a Wilcoxon signed rank test. The study was approved by the hospital ethics committee.

RESULTS

Patient characteristics are shown in table 1.

There was a decrement in the concentration of relaxin between aorta and coronary sinus in 16 of the 20 subjects

studied, suggesting cardiac extraction of relaxin. The mean (SD) concentration fell from 38.1 (61.3) pg/ml to 32.8 (57.8) pg/ml ($p < 0.04$).

No characteristic differentiated the 16 patients with cardiac extraction of relaxin from the remaining four.

There was no transpulmonary gradient in relaxin concentration. The mean (SD) concentration in the pulmonary artery was 42.0 (68.3) pg/ml *v* 41.8 (69.1) pg/ml in the pulmonary vein ($p = \text{NS}$).

DISCUSSION

Dschietzig and colleagues showed higher coronary sinus than left ventricular relaxin concentrations in 11 of 14 patients with severe CHF, suggesting that the failing heart may be a source of circulating relaxin.³ We found the opposite across the non-failing heart—that is, net extraction of relaxin. Further inspection of the data from Dschietzig and colleagues shows no transcardiac gradient in patients with moderate CHF and an aorta–coronary sinus decrement in controls, in keeping with our findings.³ This suggests that the contribution of the heart to circulating relaxin varies according to the presence or absence of CHF. Whether it is left ventricular systolic dysfunction, abnormal pulmonary or systemic haemodynamics, neurohumoral activation or other factors that leads to net cardiac secretion of relaxin in CHF is presently unknown.

The pattern of relaxin secretion/extraction is distinct from other hormones. A type and B type natriuretic peptide increase from aorta to coronary sinus in both the non-failing and failing heart (more notably in the latter).⁴ Adrenomedullin is also secreted by both the failing and non-failing heart. In contrast, endothelin-1 is extracted by the failing heart, whereas there seems to be either no transcardiac gradient or higher coronary sinus concentrations in non-failing hearts.⁵ There is no transcardiac gradient in plasma aldosterone concentration in the non-failing heart but an increment in coronary sinus aldosterone concentration in CHF.

Interpretation of the cardiac extraction of relaxin by the normal heart, compared to its secretion by the failing heart, is difficult. The mechanisms of relaxin clearance from the circulation are unknown. Changes in the transcardiac concentration of other peptides seem to reflect changes in receptor density/affinity—for example, decreases in endothelin concentration across the failing heart are probably caused by the increase in myocardial ET_A and ET_B receptors.⁶ The receptors for relaxin have only recently been described and nothing is known about the effect of CHF on their expression.¹

The transpulmonary gradient in relaxin concentration has not been described before. Neither net extraction nor secretion occurred, which is different than for other peptides. Pulmonary extraction of A type natriuretic peptide⁴ and adrenomedullin has been described. For endothelin, some have described no transpulmonary concentration gradient, others pulmonary extraction, and others still that both secretion and extraction, which balance each other out, occur.⁵ Relaxin also differs from other peptides in having no effect in small

Table 1 Characteristics of patients studied

Male/female	n=14/6
Mean (range) age (years)	62 (44–74)
Mean (range) LVEF (%)	55 (25–70)
Medical history	
Hypertension	4
Diabetes mellitus	3
Prior myocardial infarction	7
Asthma	2
Current smoker	3
Medication	
β Blocker	17
ACE inhibitor	8
Calcium channel blocker	9
Long acting nitrate	8
Nicorandil	3
HMG CoA reductase inhibitor	17
Diuretic	4

ACE, angiotensin converting enzyme; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LVEF, left ventricular ejection fraction.

pulmonary resistance arteries (whereas it is a potent vasodilator in comparable vessels from the systemic circulation).²

In summary, in patients with coronary disease but without CHF, there is net cardiac extraction of relaxin in contrast to reported secretion in CHF. In patients without CHF there is no transpulmonary gradient in relaxin.

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Authors' affiliations

C Fisher, J J V McMurray, Department of Cardiology, Western Infirmary, Glasgow, UK

S Al-Benna, A Kirk, Department of Cardiothoracic Surgery, Western Infirmary

J J Morton, Neuroendocrine Laboratory, Western Infirmary

Correspondence to: Professor John JV McMurray, Department of Cardiology, Western Infirmary, Glasgow, G12 8QQ, UK; j.mcmurray@bio.gla.ac.uk

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IMAGES IN CARDIOLOGY.....

Severe pulmonary hypertension in a patient with hypertrophic cardiomyopathy: response to alcohol septal ablation

Mild to moderate pulmonary hypertension secondary to elevation of left atrial pressure is common in patients with hypertrophic cardiomyopathy. However, severe pulmonary hypertension of systemic levels is unusual in these patients, especially in the absence of severe fixed obstruction and severe mitral regurgitation.

A 74 year old woman presented with severe exertional dyspnoea. On echocardiography, she was found to have hypertrophic obstructive cardiomyopathy with a labile left ventricular outflow tract gradient, mild to moderate mitral regurgitation, and severe pulmonary hypertension. She underwent implantation of a permanent pacemaker but continued to have severe symptoms. At the time of cardiac catheterisation, there was a labile left ventricular outflow tract gradient between 5–50 mm Hg. The mean left atrial pressure was 20 mm Hg. The pulmonary artery pressure was 100/35 mm Hg, at a time when the aortic systolic pressure was 108 mm Hg (left hand panel: LV, left ventricular pressure; Ao, aortic pressure; PA, pulmonary artery pressure; LA, left atrial pressure).

Alcohol septal ablation was performed without complications. Six months after the procedure, the patient was free of exertional symptoms. Repeat cardiac catheterisation demonstrated resolution of the left ventricular outflow tract gradient and a decrease in the mean left atrial pressure. The pulmonary artery

systolic pressure had dropped to 62 mm Hg with an aortic systolic pressure of 160 mm Hg (right hand panel).

E S Brilakis
R A Nishimura
rnishimura@mayo.edu