SCIENTIFIC LETTER

Lack of association between angiotensin converting enzyme (ACE) genotype, serum ACE activity, and haemodynamics in patients with primary pulmonary hypertension

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Primary pulmonary hypertension (PPH) is caused by progressive obliteration of the pulmonary vascular bed that leads to a right ventricular adaptive response—that is, right ventricular hypertrophy and dilatation—and eventually results in right heart failure. In patients with PPH, low cardiac output and elevated right atrial pressures are indicators of poor survival¹ and both variables are closely related to right ventricular systolic and diastolic performance. It is unknown why some patients seem to adapt quite well to elevated pulmonary vascular resistances while others develop right heart failure early in the course of their disease. Apparently, adaptation of the right heart varies substantially among individuals. The mechanisms involved in the right ventricular response to elevated pulmonary vascular resistance are unknown. Earlier studies have suggested that the angiotensin converting enzyme (ACE) genotype may be closely related to right heart function in patients with pulmonary hypertension.² The cloning of the ACE gene has led to the identification of a deletion (D)-insertion (I) polymorphism that affects the level of serum and tissue ACE activity.³ The D/D genotype is associated with the highest ACE level of activity and has been linked to left ventricular hypertrophy.⁴ This association has been attributed to increased formation of angiotensin II. However, other investigators were unable to duplicate these results.⁵

To the best of our knowledge, only one study has yet addressed ACE activity and cardiac function in patients with pulmonary hypertension. In 20 patients with PPH, Abraham and colleagues² found the D/D genotype to be more common (50%) than in the normal population (23%). More importantly, it appeared that patients who carried the D/D genotype had a more preserved cardiac function than those with the I/D or I/I genotype, suggesting that increased ACE activity might permit a greater hypertrophic adaptation of the pressure overloaded right ventricle. Despite the potential therapeutic implications of these findings, there have been no studies addressing this issue in a larger number of patients. We therefore

initiated a clinical study to compare haemodynamic variables with ACE serum activity and ACE genotype in a larger group of patients with PPH.

METHODS

We studied 51 consecutive patients (38 women and 13 men) with PPH who underwent diagnostic evaluation including right heart catheter studies at our institution. The diagnosis of PPH was established in accordance with the World Health Organization criteria. All patients suffered from New York Heart Association (NYHA) functional class III or IV disease. None of them was treated with ACE inhibitors. For the purpose of this investigation, venous blood samples were obtained during the catheter studies for ACE genotyping and assessment of ACE serum activity. Serum ACE concentrations were measured utilising a COBA MIRA automated system (Roche Diagnostics, Mannheim, Germany) and commercially available ACE reagents (Sigma Diagnostics, St Louis, Missouri, USA). ACE I/D polymorphism was determined by polymerase chain reaction (PCR) and conventional separation of amplified DNA by gel electrophoresis. This protocol has been approved by the ethics committee of Hannover Medical School and all patients gave informed consent. The data were compared with those from 200 healthy blood donors studied at our centre.

The results are expressed as mean (SD). The Wilcoxon rank sum test was used to compare haemodynamic variables in patients with the I/I genotype and those with the I/D or D/D genotype. Pearson's bivariate correlation analysis was performed to compare haemodynamic variables and ACE serum activity. The significance level was set at $p < 0.05$.

Abbreviations: ACE, angiotensin converting enzyme; I/D, insertion/deletion; NYHA, New York Heart Association; PCR, polymerase chain reaction; PPH, primary pulmonary hypertension

Table 1 ACE genotype and hemodynamic variables in 51 patients with primary pulmonary hypertension

	ACE genotype		
	D/D mean (SD) n=5	I/D mean (SD) n= 30	I/I mean (SD) n=16
Serum ACE (U/l)	45 (26)	41 (21)	24 (18)
RA (mm Hg)	7 (5)	8 (7)	8 (6)
PAPm (mm Hg)	49 (9)	53 (11)	53 (14)
CI (l/min/m ²)	1.7 (0.4)	2.1 (0.6)	1.8 (0.6)
PVR (dynes*s*cm ⁻²)	1.008 (514)	1.029 (450)	1.202 (513)

ACE, angiotensin converting enzyme; CI, cardiac index; I/D, insertion/deletion; PAPm, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RA, right atrial pressure.

RESULTS

In a normal population of 200 healthy blood donors studied at our centre, the I/I genotype was found in 25%, the I/D genotype in 50%, and the D/D genotype in 25%. In this control group the 95% confidence intervals for serum ACE activities were 7 to 33 U/l in the I/I group, 13 to 66 U/l in the I/D group, and 24 to 89 U/l in the D/D group (data not shown). In our group of 51 PPH patients the I/I genotype was found in 31%, the I/D genotype in 59%, and the D/D genotype in 10%. As shown in table 1, serum ACE activities were higher in patients with the I/D and D/D genotype compared with the I/I genotype. However, there were no differences between these genotypes with respect to haemodynamic variables and indices of right ventricular performance (table 1). In addition, our data did not reveal any significant correlations between serum ACE activity and right atrial pressure ($r = 0.43$), mean pulmonary arterial pressure ($r = 0.25$), cardiac index ($r = 0.01$), and pulmonary vascular resistance ($r = 0.18$).

DISCUSSION

In contrast to a previous study by Abraham and colleagues,² we found no evidence for an association between ACE genotype and ACE serum activity, respectively, and right ventricular performance in patients with PPH. In our study, there were no significant differences in mean pulmonary artery pressure, right atrial pressure, cardiac index or pulmonary vascular resistance between patients with the I/I, I/D, or D/D genotype, although serum ACE activities were higher in patients with an I/D or D/D genotype compared to those with an I/I genotype. In addition, we were unable to find significant associations between serum ACE activities and any haemodynamic variables in our patients.

We can only speculate on reasons why the initial results published by Abraham and colleagues² could not be reproduced in our study. The most likely explanation may be that the small number of patients in the study by Abraham and colleagues ($n = 20$) caused a sample bias. Nevertheless we

cannot fully rule out a role of the ACE system in cardiac performance since ACE serum concentrations may not adequately mimic tissue ACE activity. Furthermore, the study population may have been biased since all patients had NYHA functional class III or IV disease and patients with less severe disease caused by any protective genotype could have been under represented.

Despite these limitations, our data do not support the hypothesis that ACE activity plays a major role in adaptation of the pressure overloaded right ventricle. Further studies should address other mechanisms that may affect cardiac function in patients with PPH.

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