Angiotensin I converting enzyme genotype affects ventricular remodelling in children with aortic coarctation

M Zadinello, G Greve, X Q Liu, J R Barbosa Jr, I Schulze-Neick, J L Wilkinson, A N Redington

Angiotsin I converting enzyme (ACE) is responsible for the hydrolisation of angiotensin I into angiotensin II, which is the principal circulating hormone of the renin-angiotensin system. It was shown that angiotensin II stimulates myocardial growth by a direct effect on cardiac myocytes (increasing the fractional rate of protein synthesis), and also by indirect effects (increasing total peripheral vascular resistance). A single polymorphism of the ACE gene is described as follows: the insertion/larger allele, I, and the deletion/shorter allele, D, as well as a heterozygous form, ID, were located in intron 16 of chromosome 17q23. DD was associated with an increased plasma ACE activity and a high concentration of plasma angiotensin II. This gene polymorphism has been implicated in the pathogenesis of various cardiovascular diseases. DD has been associated with LV hypertrophy, ischaemic and idiopathic cardiomyopathy, and an increased risk of sudden death in hypertrophic cardiomyopathy. This association between increased LV mass and ACE gene polymorphism might be expected to modify the responses to congenital abnormalities, but to date no data are available. This study examines the relation between polymorphism of the ACE gene and LV remodelling in children after successful repair of aortic coarctation.

RESULTS
Forty-five patients (28 males) were enrolled in the study. Mean (SD) age at operation was 2.25 (3.25) months. Twenty-five patients (56%) had their operation within the neonatal period. Body weight at the time of surgery was 5 (2) kg; BSA was 0.24 (0.08) m². Subclavian flap repair was performed in 36 patients (80%); end to end anastomosis was performed in the remainder. Mean age at follow up was 7 (5) years. Mean follow up time was 7 (5.2) years.

Patients were grouped according to their ACE genotype. The genetic distribution was as follows: 14 patients had the DD genotype (31%), 22 patients had the ID genotype (49%), and nine patients had the II genotype (20%).

Table 1 shows the results for diastolic ventricular mass (according to the three methods) adjusted for BSA, BSA1.5, and height2.7. DD genotype was associated with increased ventricular mass when compared with II genotype. There was no difference between II and ID. However, when the II group was compared with all those with D insertion (ID + DD), the LV mass adjusted by BSA was significantly increased.

DISCUSSION
This study shows a relation between genotype and LV phenotype in the setting of congenital heart disease. We have shown that the genotype significantly affects LV mass in patients after an uncomplicated repair of aortic coarctation. Postoperatively, no patient had important residual obstruction or associated lesions and none were receiving medication for resting hypertension. In these patients the possession of the D allele, particularly DD, was associated with increased LV mass. We chose to assess LV mass using multiple algorithms because of the lack of acceptance of individual methods. Despite different techniques, there was broad agreement between them, substantiating the presence of an

Abbreviations: ASE, American Society of Echocardiography; ACE, angiotensin I-converting enzyme; BSA, body surface area; WSD, ventricular; PCR, polymerase chain reaction; PWD, posterior wall in diastole

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important LV hypertrophic response. The importance of our findings lies in the potential influence of ACE genotype on adverse cardiovascular events.

Whether this represents failure of regression of a previous hypertrophic response or reflects an abnormal hypertrophic response in the setting of chronically abnormal haemodynamics, cannot be answered by our data. Most evidence would favour the latter. Despite adequate repair, endothelial function in the upper body is abnormal, and our own recent data suggest a persistently increased arterial stiffness in teenagers and adults.

ACE genotype seems to influence the incidence of cardiac events independent of structural abnormalities (for example, cardiomyopathies). The combination of adverse ACE genotype and a haemodynamic stimulus may amplify these adverse effects. While speculative, knowledge of ACE genotype may identify or help to refine risk stratification in those at risk from long term cardiovascular morbidity. Furthermore, knowledge of genotype may increase understanding of the need for, and response to, treatment of resting, exercise or ambulatory hypertension, the management of which remains controversial in these patients.

In summary, this is the first study to demonstrate the influence of ACE genotype on ventricular phenotype in patients with congenital heart disease. Possession of the D allele, both in heterozygotes, but particularly homozygotes, predicts increased LV mass after successful repair of aortic coarctation. This may have important implications for the long term cardiovascular mortality in these patients.

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