

## SCIENTIFIC LETTER

Confirmation of a role for the 389R>G  $\beta$ -1 adrenoceptor polymorphism on exercise capacity in heart failure

A J Sandilands, J Parameshwar, S Large, M J Brown, K M O'Shaughnessy

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The  $\beta$ -1 adrenoceptor (AR), and to a lesser extent the  $\beta$ -2 AR, mediate the effect of circulating catecholamines on the pumping efficiency of the heart through positive inotropic, chronotropic, and lusitropic effects. These responses are required to meet the demands for increased tissue blood flow, not only during exercise, but also in pathophysiological states such as heart failure. Yet, cardiac responsiveness to  $\beta$ -1 AR activation or blockade, especially in heart failure, displays significant variation between individuals.<sup>1</sup> The discovery of two common polymorphisms within the  $\beta$ -1 AR gene supports the notion that part of this may be genetic in origin. These variants, 389R>G and 49S>G, affect the encoded amino acid sequence (switching arginine to glycine and serine to glycine, respectively) and have notable effects on  $\beta$ -1 AR signalling both in cell lines and in intact human myocardial tissue.<sup>2,3</sup> In vivo, the failing myocardium with its down regulated  $\beta$ -1 AR function may be particularly affected by these polymorphisms. Here we confirm a previous report that heart failure patients awaiting transplant do have significantly different exercise capacities depending on their genotype status for the 389R>G  $\beta$ -1 AR polymorphism.

## PATIENTS AND METHODS

To identify sufficient numbers of patients with severe left ventricular (LV) dysfunction, we retrospectively approached 167 living patients entered into the cardiac transplant programme between 1993 and 2002 at Papworth Hospital, Cambridge. They were invited by letter to take part in the study and had completed a standard exercise test as part of their cardiac transplant assessment. A total of 83 patients gave informed consent and a blood sample for DNA extraction. There were 13 females and 70 males with a diagnosis of either ischaemic (n = 36) or idiopathic dilated cardiomyopathy (n = 47). At diagnosis, the mean age was 50.9 (8) years with left ventricular ejection fraction (LVEF) of 19 (1)%. Medications at the time of exercise testing were recorded, but were not changed for the purpose of carrying out the exercise testing. The Huntingdon local research ethics committee approved the study. The 389R>G and 49S>G genotypes of the  $\beta$ -1 AR were determined using polymerase chain reaction/restriction fragment length polymorphism.<sup>2</sup> The protocol for the exercise test was the steep treadmill.<sup>4</sup> Patients were accustomed to the respiratory gas analyser in the sitting position followed by one minute standing, then a warm up period of two minutes leading to exercise with increases in speed and gradient until patient exhaustion. Heart rate,  $\text{Vo}_2$ , and exercise time were recorded. All results are expressed as the mean (SEM) except age which was standard deviation. Comparison of the variables studied by genotype were analysed by analysis of variance (ANOVA) followed by post hoc comparisons or multiple regression models using the SPSS package (version 11) as appropriate. Significance was taken as  $p < 0.05$ . Based on previous differences in  $\text{Vo}_2$  reported between GG and RR (14.5–17.7 ml/kg/min),<sup>5</sup> we estimated our sample to have at least 80% power to detect a similar difference.

## RESULTS

The genotype frequencies of the 83 patients were similar to those previously published: RR 0.47, RG 0.45, GG 0.08,<sup>1</sup> and SS 0.76, SG 0.23, GG 0.01.<sup>2</sup> Patient demographics stratified by genotype were well matched for age, sex, height, weight, aetiology of failure, lung function, LVEF, and medications. These are displayed in table 1 by genotype. Peak  $\text{Vo}_2$  and exercise time were significantly greater for patients homozygous for 389R compared to homozygote 389G patients. This significant effect on peak  $\text{Vo}_2$  also remained after correction for confounding factors including age, treatment with  $\beta$  blockers, and LVEF ( $p = 0.029$ ). Because of the potential functional interaction between both common polymorphisms, 49 S homozygotes were also studied separately. Peak  $\text{Vo}_2$  still remained significantly higher for 389R homozygotes (n = 28) compared to either 389G homozygotes (n = 6), or 389G carriers (GG homozygotes and RG heterozygotes, n = 35); 16.5 (1.2) v 10.8 (1.1) ml/kg/min,  $p = 0.002$ , and 16.5 (1.2) v 13.4 (0.8) ml/kg/min,  $p = 0.027$ , respectively. Heart rate was not different between any of the groups. For the 49S>G polymorphism, SS homozygotes were compared to 49G carriers because of the paucity of 49G homozygotes and were identical to the 49G carriers for all exercise parameters.

## DISCUSSION

This work demonstrates that among patients with severe heart failure, R389 homozygotes have significantly enhanced exercise performance compared to G389 homozygotes. This is in keeping with the behaviour of the 389  $\beta$ -1 AR variants, both in cell lines and isolated human myocardial tissues.<sup>2,3</sup> The 389R variant generates cyclic AMP concentrations threefold higher than the 389G variant in transfected HEK 293 cells.<sup>3</sup> Similarly, in human atrial myocardium, noradrenaline (norepinephrine) generates both greater inotropic and cyclic AMP responses via the 389R variant compared to the 389G variant.<sup>2</sup>

Our recruited population consisted mainly of males, as did the study population reported by Wagoner *et al.*<sup>5</sup> In our patients, this reflects the sex ratio (4:1) among patients transplanted on the Papworth Hospital programme itself. Our results confirm the Wagoner study, although the differences between 389R and 389G homozygotes in our study were somewhat larger than they reported.<sup>5</sup> This may reflect the lower LVEF seen in our subjects ( $\leq 20\%$  v  $> 25\%$  in the Wagoner cohort) and presumably more diseased myocardial tissue. It is well documented that the degree of uncoupling of the  $\beta$ -1 AR increases with failure, which may enhance the functional separation between the 389R and 389G receptor variants in vivo. However, unlike our study, Wagoner and *et al.* reported that the 49S>G polymorphism also affected exercise performance.<sup>5</sup> Since we did not power our study to address this rarer polymorphism, our finding with 49S>G may represent a false negative.

**Abbreviations:** AR, adrenoceptor; LV, left ventricular; LVEF, left ventricular ejection fraction

**Table 1** Demographics and exercise parameters in patients stratified by  $\beta$ -1 AR genotype

	GG 389 (n = 7)	RG 389 (n = 37)	RR 389 (n = 39)	SS 49 (n = 63)	SG/GG49 (n = 20)
Age	54.1 (3.1)	50.5 (9.5)	50.6 (7.0)	51.0 (8.2)	50.3 (7.3)
% Female	14.3	18.9	20.5	17.4	15.0
LVEF	16.1 (3)	19.2 (1.1)	21.2 (1.7)	18.8 (1.1)	19.7(2)
Peak $\dot{V}O_2$	11.1 (1.0)*	13.9 (0.7)†	16.5 (1.1)	14.8 (0.7)	15.1 (1.2)
Peak heart rate	129 (11)	124 (5)	125 (4)	125 (3)	123 (6)
Exercise time	5.3 (0.8)‡	6.3 (0.4)	7.2 (0.4)	6.4 (0.4)	6.8 (0.6)

\* $p < 0.001$  v RR homozygotes and  $p < 0.05$  v heterozygotes; † $p < 0.05$  v RR homozygotes; ‡ $p < 0.05$  v RR homozygotes.

In summary, this study confirms the importance of the 389R>G  $\beta$ -1 AR polymorphism in patients with severe LV dysfunction. Given the interplay of the 389R>G and 49S>G  $\beta$ -1 AR receptor variants in vitro,<sup>3</sup> further studies are needed to define the role of individual 389/49  $\beta$ -1 AR haplotypes in patients with severe heart failure.

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### Authors' affiliations

**A J Sandilands, M J Brown, K M O'Shaughnessy**, Department of Clinical Pharmacology, University of Cambridge, Cambridge, UK  
**J Parameshwar, S Large**, Heart and Lung Transplant Unit, Papworth Hospital, Cambridge, UK

Correspondence to: Dr Alastair J Sandilands, Cardiac Department, Great Western Hospital, Swindon SN3 6BB, UK; ajs90@doctors.org.uk

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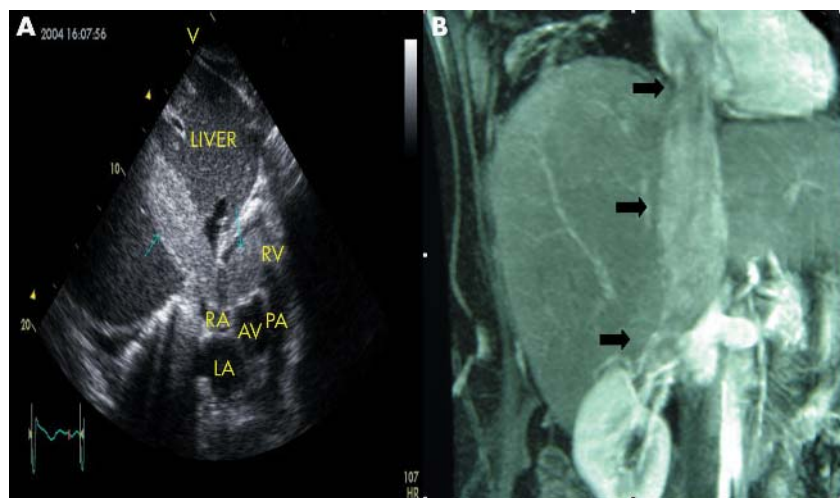
## IMAGES IN CARDIOLOGY

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### Kidney cancer with cardiac extension

**A** 70 year old woman presented to the emergency department with dyspnoea and fever of a few weeks duration. Transthoracic echocardiography revealed a mass extending from the inferior vena cava to the right ventricle, with prolapse through the tricuspid valve (panel A). Magnetic resonance imaging (MRI) confirmed that the mass originated from the superior pole of the right kidney (panel B). The mass was successfully resected in two segments via a thoracic and abdominal approach. Histologic examination confirmed that the lesion was a clear cell carcinoma. The patient was discharged from the hospital 18 days after surgery.

F Haziza  
D Tixier  
T Lebret  
f.haziza@hopital-foch.org



Panel A. Transthoracic echocardiography subcostal small axis view (blue arrow, tumour; AV, aortic valve; LA, left atrium; PA, pulmonary artery; RA, right atrium; RV, right ventricle). Panel B: Magnetic resonance image. Development of the tumour (black arrows) from the right kidney, through the inferior vena cava toward the heart.