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

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


The β-1 adrenoceptor (AR), and to a lesser extent the β-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 β-1 AR activation or blockade, especially in heart failure, displays significant variation between individuals.1 The discovery of two common polymorphisms within the β-1 AR gene supports the notion that part of this variation may be genetic in origin. These variants, 389R–G and 495S–G, affect the encoded amino acid sequence (switching arginine to glycine and serine to glycine, respectively) and have notable effects on β-1 AR signalling both in cell lines and in intact human myocardial tissue.2-3 In vivo, the failing myocardium with its down regulated β-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 β-1 AR polymorphism.

RESULTS

The genotype frequencies of the 83 patients were similar to those previously published: RR 0.47, RG 0.45, GG 0.08,1 and SS 0.76, SG 0.23, GG 0.01.2 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 VO2 and exercise time were significantly greater for patients homozygous for 389R compared to homozygote 389G patients. This significant effect on peak VO2 also remained after correction for confounding factors including age, treatment with β blockers, and LVEF (p = 0.029). Because of the potential functional interaction between both common polymorphisms, 49S homozygotes were also studied separately. Peak VO2 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 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 β-1 AR variants, both in cell lines and isolated human myocardial tissues.2 The 389R variant generates cyclic AMP concentrations threefold higher than the 389G variant in transfected HEK 293 cells.1 Similarly, in human atrial myocardium, noradrenaline (norepinephrine) generates both greater inotropic and cyclic AMP responses via the 389R variant compared to the 389G variant.2

Our recruited population consisted mainly of males, as did the study population reported by Wagoner et al.1 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.1 This may reflect the lower LVEF seen in our subjects (<20% v >25% in the Wagoner cohort) and presumably more diseased myocardial tissue. It is well documented that the degree of uncoupling of the β-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.3 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
In summary, this study confirms the importance of the 389R>G β-1 AR polymorphism in patients with severe LV dysfunction. Given the interplay of the 389R>G and 49S>G β-1 AR receptor variants in vitro, further studies are needed to define the role of individual 389/49 β-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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REFERENCES


Table 1: Demographics and exercise parameters in patients stratified by β-1 AR genotype

<table>
<thead>
<tr>
<th></th>
<th>GG 389 (n = 7)</th>
<th>RG 389 (n = 37)</th>
<th>RR 389 (n = 39)</th>
<th>SS 49 (n = 63)</th>
<th>SG/GG49 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.1 (3.1)</td>
<td>50.5 (9.5)</td>
<td>50.6 (7.0)</td>
<td>51.0 (8.2)</td>
<td>50.3 (7.3)</td>
</tr>
<tr>
<td>% Female</td>
<td>14.3</td>
<td>18.9</td>
<td>20.5</td>
<td>17.4</td>
<td>15.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>16.1 (1.3)</td>
<td>19.2 (1.1)</td>
<td>21.2 (1.7)</td>
<td>18.8 (1.1)</td>
<td>19.7 (2)</td>
</tr>
<tr>
<td>Peak VO2 (ml/kg/min)</td>
<td>11.3 (1.0)*</td>
<td>13.9 (0.7)*</td>
<td>16.5 (1.1)</td>
<td>14.8 (0.7)</td>
<td>15.1 (1.2)</td>
</tr>
<tr>
<td>Peak heart rate</td>
<td>129 (11)</td>
<td>124 (5)</td>
<td>125 (4)</td>
<td>125 (3)</td>
<td>123 (6)</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>5.3 (0.8)</td>
<td>6.3 (0.4)</td>
<td>7.2 (0.4)</td>
<td>6.4 (0.4)</td>
<td>6.8 (0.6)</td>
</tr>
</tbody>
</table>

*p<0.001 v RR homozygotes and p<0.05 v heterozygotes; t*p<0.05 v RR homozygotes; t*p<0.05 v RR homozygotes.

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.

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.

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

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