Polymorphisms of the β2-Adrenergic Receptor Determine Exercise Capacity in Patients With Heart Failure


Abstract—The β2-adrenergic receptor (β2AR) exists in multiple polymorphic forms with different characteristics. Their relevance to heart failure (HF) physiology is unknown. Cardiopulmonary exercise testing was performed on 232 compensated HF patients with a defined β2AR genotype. Patients with the uncommon Ile164 polymorphism had a lower peak VO2 (15.0±0.9 mL·kg⁻¹·min⁻¹) than did patients with Thr164 (17.9±0.9 mL·kg⁻¹·min⁻¹, P<0.0001). The percentage achieved of predicted peak VO2 was also lower in patients with Ile164 (62.3±4.5% versus 71.5±5.1%, P=0.045). The relative risk of a patient having a VO2 ≤14 mL·kg⁻¹·min⁻¹ who had Ile164 was 8.0 (P=0.009). Catheterization-based invasive exercise testing revealed depressed changes in the exercise-induced cardiac index, systemic vascular resistance, stroke volume, and VO2 in patients with Ile164. The polymorphisms at position 16 also impacted exercise capacity: peak VO2 for Arg16 versus Gly16 was 17.0±0.8 versus 15.6±0.5 mL·kg⁻¹·min⁻¹, respectively (P=0.03). Because the polymorphisms at loci 16 and 27 can occur together, 4 homozygous combinations exist. Patients with Arg16/Glu27 had the highest percentage achieved of predicted peak VO2 (75.7±6.4%), whereas those with Gly16/Gln27 had the lowest (55.3±2.8%, P=0.0032). The above findings were not confounded by baseline clinical characteristics, including β-blocker usage. We conclude that the β2AR polymorphisms Ile164, Gly16, and the combination of Gly16 and Gln27 are associated with depressed exercise performance in HF and represent a genetically determined factor in the pathophysiology of HF. (Circ Res. 2000;86:834-840.)

Key Words: exercise • heart failure • β2-adrenergic receptors • genetics

The sequence of the human β2-adrenergic receptor (β2AR) gene is highly variable, giving rise to a coding region with numerous genetic polymorphisms (Figure 1).1–3 Of particular interest, 3 polymorphic β2ARs exhibit altered receptor function in in vitro expression assays. As a common frame of reference, the β2AR containing Arg16, Gln27, and Thr164 is considered to be a “wild type” (although Gly at position 16 appears to be more frequent than Arg).1 Compared with the wild types, β2ARs with the following substitutions exhibit abnormal receptor-effector coupling or patterns of desensitization: Gly versus Arg at amino acid position 16, Gln versus Gln at position 27, and Ile versus Thr at position 164.

When recombinantly expressed in Chinese hamster fibroblasts or studied as the endogenous polymorphic receptor in human airway smooth muscle cells, Gly16 β2ARs show enhanced agonist-promoted receptor downregulation.3 In contrast, the Gln27 polymorphic receptor undergoes little or no downregulation under similar conditions.3 Although the mechanism of altered downregulation imposed by these variations is not entirely clear, our studies have indicated that modified receptor degradation after internalization is the basis of these phenotypes.3 As predicted from their location in the extracellular terminus, coupling of these polymorphic receptors to stimulation of adenylyl cyclase is not modified. However, evidence suggests that endogenous catecholamines are sufficient to induce the different downregulation phenotypes2; thus, receptor function is, in fact, altered by the amino-terminal polymorphism (Gly16 has depressed and Gln27 has enhanced function compared with wild-type function). In contrast to these amino-terminal polymorphisms, the Ile164 receptor has decreased basal and agonist-stimulated adenylyl cyclase activities and decreased affinity for agonists and some antagonists.2 This receptor also downregulates, so it has the potential to have the most severe phenotype of the 3 polymorphisms. Transgenic mice overexpressing this polymorphic β2AR in the heart exhibit depressed inotropy and chronotropy.3

In considering the pathophysiological consequences of polymorphic β2ARs, it is important to note that β2ARs are highly expressed throughout the cardiovascular system, in which they mediate increased myocardial inotropy and chronotropy5 and arterial vasodilation. Downregulation of the myocardial β1-adrenergic receptor in heart failure (HF) and...
the resulting increase in relative cardiac β2AR expression suggest that cardiac β2AR expression and function are of particular importance in this condition.6 Consistent with this notion, our prior studies in HF have demonstrated that genetic variability of β2ARs is one determinant of disease progression. Patients with Ile164 progress more rapidly to death or transplantation than those with Thr164. Strong trends were also seen with Gly16 or Gln27 (both of which have increased downregulation compared with their counterparts).7

Exercise capacity is a critical determinant of prognosis in HF patients. Indeed, exercise capacity measured by peak VO2 during cardiopulmonary exercise testing (CPX) with respiratory gas analysis predicts survival in patients with HF.8 Moreover, a significant deterioration of maximal exercise performance frequently precedes clinical decompensation.9 Also, peak VO2 and exercise duration are correlated with overall cardiac β-adrenergic receptor density in patients with mild to moderately severe HF due to idiopathic dilated cardiomyopathy.10 Thus, we considered that if β2AR polymorphisms are disease modifiers in congestive HF, clinically compensated patients bearing these polymorphisms should exhibit different cardiovascular responses to exercise. Specifically, we hypothesized that the patients with the polymorphism Ile164 would have significantly depressed responsiveness to exercise and that, to a lesser extent, those with Gly16 and/or Gln27 would have depressed responsiveness compared with those with Arg16 and/or Glu27. In the present study, we describe the effect of these β2AR polymorphisms on the outcome of CPX in 232 clinically compensated congestive HF patients with idiopathic dilated or ischemic cardiomyopathies.

Materials and Methods

Patients

The study was approved by the Institutional Review Board of the University of Cincinnati. Two hundred thirty-two unrelated sequential patients (73% male, 80% white and 20% African American, aged 49.5 ± 6 years) with ischemic cardiomyopathy (n = 84) or idiopathic dilated cardiomyopathy (n = 148), New York Heart Association functional class (NYHA FC) II to IV, and left ventricular ejection fraction (LVEF) 26.7 ± 0.9% were genotyped for β2AR polymorphism, with genomic DNA used as a template. All patients were stable on HF therapy and were ambulatory. Pertinent medications and frequency of use at the time of the exercise test included digoxin (93.9%), diuretics (92.1%), β-blockers (24.9%), angiotensin-converting enzyme inhibitors (90.0%), angiotensin II receptor blockers (9.6%), and amiodarone (17.5%).

β2AR Genotyping

Genomic DNA was isolated from peripheral blood. β2AR genotyping was carried out with the use of the genetic bit analysis method.7

Cardiopulmonary Exercise Testing

Patients underwent CPX on a treadmill (Medgraphics); a Modified Naughton protocol was used. VO2 (mL/min), VCO2 (mL/min), and minute ventilation (L/min) were measured continuously. VO2 was normalized for body mass (VO2, mL ⋅ kg⁻¹ ⋅ min⁻¹). Pertinent exercise parameters included peak VO2, VO2 at anaerobic threshold, VO2 at a respiratory exchange ratio (RER) of 1, VO2 divided by the predicted maximum (%Max VO2), metabolic equivalents at peak exercise, and exercise time.

Invasive Exercise Hemodynamic Testing

Twelve patients (6 with Ile164 and 6 with Thr164) were enrolled in an invasive assessment of exercise hemodynamics. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and calcium channel blockers were held for 48 hours. A Swan-Ganz catheter (Baxter CCO/VO2) was positioned in the pulmonary artery (PA). A catheter was inserted into the radial artery. Thirty minutes later, baseline hemodynamic measurements were made of PA pressure, pulmonary capillary wedge pressure (PCWP), central venous pressure, and systemic pressures. Cardiac output was calculated by using the Fick equation with arterial saturation obtained from pulse oximetry and PA saturation from the sV02 catheter. Patients exercised to symptomatic maximum with use of a bicycle ergometry protocol. Respiratory gas and heart rate measurements were made continuously; hemodynamic measurements and arterial and PA saturations were recorded at every 2 minutes of exercise, at peak exercise, and at 1, 3, and 5 minutes of recovery.

Statistical Methods

Because of the low frequency of the Ile164 allele in the population,7 we paired in a blinded fashion all 18 patients exhibiting Ile164 with Thr164. The characteristics of patients with the Ile164 polymorphism, with genomic DNA used as a template. All patients were stable on HF therapy and were ambulatory. Pertinent medications and frequency of use at the time of the exercise test included digoxin (93.9%), diuretics (92.1%), β-blockers (24.9%), angiotensin-converting enzyme inhibitors (90.0%), angiotensin II receptor blockers (9.6%), and amiodarone (17.5%).

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Table 2 shows the exercise parameters of patients with Ile164 compared with Thr164. As predicted, patients with Ile164 had a lower peak $\dot{V}O_2$ (15.0±0.9 mL·kg$^{-1}$·min$^{-1}$) than patients with Thr164 (17.9±0.9 mL·kg$^{-1}$·min$^{-1}$, $P=0.0004$, unadjusted). Potential confounders were added into the statistical model as indicated above. The only factor found to be a significant confounder was the genotype of the $\beta_2$AR at position 16 ($P=0.003$), and after adjustment, the difference in the peak $\dot{V}O_2$ was even more statistically significant ($P<0.0001$). Importantly, $\beta$-blocker usage, which was similar in both groups, was not a confounder. Also, %Max $\dot{V}O_2$ was significantly lower in the patients with Ile164 compared with those with Thr164 (62.3±4.5% versus 71.5±5.1%; $P=0.045$, adjusted) as was $\dot{V}O_2$ at RER 1 (12.1±0.8 versus 13.8±0.8 mL·kg$^{-1}$·min$^{-1}$; $P=0.045$, adjusted). These significant differences did not result from differing exercise levels or motivation; the patients in both groups achieved equivalent maximum RER and maximum heart rate at peak exercise. Identical peak heart rates occurred in the 2 groups. No differences were found in baseline or maximum systolic or diastolic blood pressure. Furthermore, we calculated the relative risk of having a peak $\dot{V}O_2 \leq 14$ mL·kg$^{-1}$·min$^{-1}$ (a clinically accepted value that indicates a lower 1-year survival rate$^8$) if the Ile164 receptor is present. We found the risk to be 8.0 ($P=0.009$).

Six patients with the Ile164 receptor (aged 57.7±3.6 years, LVEF 20.0±3.7%) and 6 patients with the Thr164 receptor (aged 52.8±3.9 years, LVEF 25.5±4.1%) underwent invasive exercise hemodynamic testing. Consistent with the noninvasive studies (Tables 1 and 2), baseline cardiac output,
cardiac index, heart rate, stroke volume, and systemic vascular resistance (SVR) were not different between the 2 groups (data not shown). Exercise-induced changes were significantly lower in patients with Gly16 for VO\textsubscript{2}, stroke volume, cardiac index, and SVR (Figure 2). No differences in heart rate, PA systolic or diastolic pressures, PCWP, or systemic diastolic or diastolic pressures were noted.

On the basis of our previous in vitro studies in which Gly16 \(\beta\)-ARs show enhanced receptor downregulation, we hypothesized that individuals bearing the homozygous Gly16 receptor would have reduced exercise capacity compared with individuals with homozygous Arg16. We excluded patients who were heterozygous at position 16 and patients with Ile16 from this analysis. Thus, the results from 74 patients bearing the Gly16 receptor and 44 patients with Arg16 were analyzed. The characteristics of patients homozygous for Gly16 and Arg16 are shown in Table 1.

As shown in Table 3, patients expressing Gly16 had a lower peak VO\textsubscript{2} (15.6 ± 0.5 versus 17.0 ± 0.8 mL \cdot kg\(^{-1}\) \cdot min\(^{-1}\); \(P=0.045\), unadjusted). Again, no significant difference was noted in the maximum RER and maximum heart rate at peak exercise, indicating no difference in exercise effort during the tests. Potential confounders were added into the statistical model; age (\(P=0.0001\)), sex (\(P=0.002\)), and race (\(P=0.02\)) were significant confounders, whereas \(\beta\)-blocker usage was not. When the data were reanalyzed with these confounders taken into account, the difference in peak VO\textsubscript{2} between Arg16 and Gly16 was significant (\(P=0.03\), adjusted). The %Max VO\textsubscript{2} was also lower with Gly16 compared with Arg16 (62.2 ± 2.1% versus 69.1 ± 2.7%, \(P=0.045\)). The results were unchanged after deleting those patients on \(\beta\)-blocker therapy at the time of the exercise test, consistent with medication use not being a confounder in the whole population analysis. No statistically significant differences in exercise parameters were noted for the individuals homozygous for the Gln27 receptor, which undergoes some degree of downregulation compared with the Glu27 polymorphism, which does not (data not shown).

Because the polymorphisms at loci 16 and 27 frequently occur together, 4 different homozygous combinations are possible. To examine the effects that the polymorphisms at positions 16 and 27 would have in combination, we analyzed the exercise parameters for the 76 patients with homozygous combinations. We hypothesized that patients expressing receptors in which both have less downregulation (Arg16/Glu27) would demonstrate an exercise capacity higher than that in patients expressing receptors in which both are highly sensitive to downregulation (Gly16/Gln27). The patients with a heterozygous receptor at either position 16 or 27 were excluded because of the potential for intermediate effects. The clinical characteristics of patients with the combinations for loci 16 and 27 were not significantly different between groups (data not shown). The exercise parameters were analyzed by use of a multiple regression model. Significant confounders included age (\(P=0.0001\)), dilated cardiomyopathy (\(P=0.0041\)), sex (\(P=0.0002\)), and race (\(P=0.0072\)). Figure 3 demonstrates the %Max VO\textsubscript{2} for all 4 combinations. The patients with Arg16/Glu27, which is the rarest combination, had the highest %Max VO\textsubscript{2} (75.7 ± 6.4%), whereas the patients with Gly16/Gln27 had the lowest %Max VO\textsubscript{2} (55.3 ± 2.8%; \(P=0.0032\) by ANOVA, adjusted). The patients with Arg16/Gln27 and Gly16/Glu27 demonstrated %Max VO\textsubscript{2} values that were intermediate to the other 2 groups. A similar pattern was noted for maximum VO\textsubscript{2} (18.6 ± 1.7 mL \cdot kg\(^{-1}\) \cdot min\(^{-1}\) for Arg16/Glu27 compared with 16.3 ± 1.1 mL \cdot kg\(^{-1}\) \cdot min\(^{-1}\) for Gly16/Gln27), but this did not reach statistical significance (\(P=0.09\), adjusted).

Discussion

The present study demonstrates that HF patients with the hypofunctional \(\beta\)-AR adrenergic receptor caused by the fourth transmembrane domain Ile164 polymorphism have a significantly lower peak VO\textsubscript{2} during treadmill exercise testing, ie, diminished exercise capacity, than do patients with Thr164. With invasive studies, these individuals were found to have depressed inotropic and vascular responses to exer-

<table>
<thead>
<tr>
<th>Exercise Parameter</th>
<th>Gly16 (n=74)</th>
<th>Arg16 (n=44)</th>
<th>Adjusted (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO\textsubscript{2}, mL \cdot kg(^{-1}) \cdot min(^{-1})</td>
<td>15.6 ± 0.5</td>
<td>17.0 ± 0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>%Max VO\textsubscript{2}, %</td>
<td>62.2 ± 2.1</td>
<td>69.1 ± 2.7</td>
<td>0.045</td>
</tr>
<tr>
<td>VO\textsubscript{2} at RER 1, mL \cdot kg(^{-1}) \cdot min(^{-1})</td>
<td>13.3 ± 0.4</td>
<td>14.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>VO\textsubscript{2} at AT, mL \cdot kg(^{-1}) \cdot min(^{-1})</td>
<td>10.8 ± 0.5</td>
<td>11.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise time, min</td>
<td>9.3 ± 0.5</td>
<td>9.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum RER</td>
<td>1.11 ± 0.01</td>
<td>1.08 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline HR, bpm</td>
<td>84 ± 1.6</td>
<td>84 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum HR, bpm</td>
<td>133 ± 1.9</td>
<td>130 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg</td>
<td>118 ± 3</td>
<td>116 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline diastolic BP, mm Hg</td>
<td>76 ± 2</td>
<td>75 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum systolic BP, mm Hg</td>
<td>142 ± 4</td>
<td>142 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum diastolic BP, mm Hg</td>
<td>84 ± 2</td>
<td>79 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>49.2 ± 1.3</td>
<td>50.1 ± 1.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are adjusted mean ± SEM.
The basis for interindividual variability in the severity or progression of HF is largely unexplained but may relate to the fact that clinical “heart failure” is the common end point for numerous diverse disease processes, each with distinct characteristic pathophysiologies. Genetic variability in disease-related genes, such as βAR, further act as disease modifiers. Thus, progression and therapeutic response in HF are likely determined by a complex interplay of intrinsic genetic characteristics and extrinsic pathogenic factors. In the present study, we have focused on the βAR, which has 3 polymorphic loci in its coding region. These 3 βAR polymorphisms have previously undergone detailed characterization as to their signaling phenotypes, providing both a structural and functional basis for clinical studies of these particular receptor variants. The Gly16 “polymorphism” is actually more common (allele frequency of \( \approx 0.60 \)) than the “wild-type” receptor, which is so designated because of the original cloning of the receptor. Site-directed mutagenesis was used to create, in vitro, this and other polymorphisms and to generate plasmid constructs for permanent expression in transfected Chinese hamster fibroblasts. As expected from its position in the amino-terminus, the Gly16 receptor had normal agonist- and antagonist-binding affinities, coupling to \( G_o \) and stimulation of adenylyl cyclase. However, compared with the wild-type receptor, this receptor exhibited enhanced sensitivity to agonist-promoted downregulation because of increased degradation after apparently normal receptor internalization. These functional characteristics were confirmed in human airway smooth muscle cells naturally expressing the Arg16 or Gly16 alleles. Similar studies have also established the characteristics of the Glu27 variant, the allelic frequency of which is \( \approx 0.40 \). This polymorphic receptor has impaired homologous downregulation in either transfected or endogenously expressing cells. In asthma, airway β2AR polymorphisms at 16 and 27 confer differences in airway reactivity and in the response to β-agons into agonists. These indicate that the receptors have the capacity to be differentially regulated by endogenous catecholamines.

Compared with the amino-terminal polymorphisms, the Ile164 receptor is uncommon, with a frequency of the heterozygous polymorphism of \( \approx 0.05 \). In vitro expression of Ile164 has shown that compared with the wild-type receptor, the polymorphic receptor has decreased agonist-binding affinities but normal affinities for most β-adrenergic receptor antagonists. The Ile164 receptor has a substantially impaired basal and agonist-stimulated coupling to adenylyl cyclase, which we have found is due to an altered receptor conformation that results in a loss of high-affinity receptor-Gs interaction. In vivo cardiomyocyte-specific expression of this receptor in transgenic mice confirmed lower basal and isoproterenol stimulated adenylyl cyclase activity for this receptor, resulting in lower resting heart rates and inotropic and lusitropic indices.

These β2AR polymorphisms have been studied within the context of disease modification of asthma and hypertension. In asthma, a disease in which these polymorphisms have been the most extensively studied, most, but not all, studies have shown a disease-modifying effect. The differences in the study designs and, in some studies, relatively small patient numbers may be the basis for some of this inconsistency. In regard to cardiovascular disease, the polymorphism at position 16 has been associated with hypertension. However, in African Caribbeans, hypertension was associated with the Gly16 variant, whereas in Norwegians, an association was found with Arg16. The designs of these 2 studies were quite different; thus, the association of hypertension with β2AR polymorphisms remains unclear.

In the present study, we have focused on the potential modifying roles of the genetic variants at position 164 on exercise performance because of its clinical relevance in HF and its relationship to catecholamine responsiveness. Peak \( \text{VO}_2 \) and/or percentage achieved of predicted peak oxygen uptake (\( \% \text{Max} \text{VO}_2 \)) are excellent predictors of survival in patients with HF. Patients with a peak \( \text{VO}_2 \) of \( \leq 14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) obtained by CPX have a reduced survival rate at 1 year (70%) compared with patients with a peak \( \text{VO}_2 > 14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) (94%); thus, peak \( \text{VO}_2 \) has become an established parameter for cardiac transplant listing. On the basis of the aforementioned in vitro and human data, we postulated that patients with the hypofunctional Ile164 β2AR would have substantially lower peak \( \text{VO}_2 \) with exercise than patients with Thr164. Markedly lower peak \( \text{VO}_2 \) was demonstrated in HF patients with Ile164 than in matched controls (15.0 versus 17.9 \( \text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)), leading us to a potential...
mechanism for decompensation in patients with this polymorphism of the β2AR. This difference in peak VO2 could not be explained on the basis of age, sex, NYHA FC, medication usage, exercise effort levels, or peak exercise heart rates. An equal number of patients in each group were being treated with β-blockers (4 of 18 in the Ile164 group [3 treated with carvedilol and 1 with metoprolol] and 3 of 18 in the Thr164 group [2 treated with carvedilol and 1 with metoprolol], and β-blocker use was not a confounder in the analysis. Furthermore, our invasive exercise hemodynamics demonstrating a lower exercise-induced cardiac index, stroke volume, and SVR in patients with Ile164 confirm that the difference in exercise parameters observed with noninvasive CPX are indeed cardiovascular effects. Of note, in these invasive studies, the patients had been withdrawn from β-blockers before the study.

This significant impact on cardiac physiology was present in individuals who are heterozygous for the Ile164 receptor. We would predict that the impairment would be of even greater magnitude in individuals homozygous for the polymorphism. However, we have not, to date, identified an individual (patient or normal) who is homozygous. Of note, the altered responses of the heterozygous patients averaged 53% of the response of those with the homozygous wild-type receptor, consistent with the notion that those with homozygous Ile164 would display little responsiveness.

Regarding the amino-terminal polymorphisms, we postulated that patients with Arg16 and/or Glu27 would exhibit the least degree of downregulation and, thus, the highest peak VO2 with exercise testing; similarly, patients with Gly16 and/or Gln27 would have a greater degree of downregulation and, thus, lower peak VO2. When analyzed as individual loci, those patients with Gly16 demonstrated lower peak VO2 than did patients with Arg16. When all 4 of the genotypic combinations were considered, it was apparent that those with Gly16/Gln27 had the lowest %Max VO2 compared with the other combinations. The magnitude of difference observed (∼20 percentage points; see Figure 2) is not only highly statistically significant, but it is also clinically relevant, especially when assessing a patient for listing for cardiac transplantation. On the basis of the %Max VO2, those patients with Gly16/Gln27 with a %Max VO2 of 55% fall into a range that would qualify them for being listed for cardiac transplantation, whereas those with Arg16/Glu27 with a %Max VO2 of 76% would not be listed.16

Our results indicating that genotypes including Ile164, Gly16, and Gly16/Gln27 adversely impact survival and/or exercise performance suggest that β2AR genotyping may be a useful test in patients with HF. Potentially, then, patients identified with these genotypes during their clinical evaluation should be considered for aggressive management with pharmacological therapy even in the early stages and also considered for transplant listing. Furthermore, various pharmacological therapies for HF, such as β-blockers, may prove to be more or less effective in patients with various β2AR genotypes. This awaits explicit testing.

The present study is limited by the influence that numerous factors exert on maximal exercise performance, including age, sex, the condition of the skeletal muscles, medications, lung disease, and patient/operator motivation.17,18 A number of these factors, including age, sex, and medication (particularly β-blockers), have been addressed by adding these factors to our general linear model. Another limitation is the small size of the Ile164 and Arg16/Glu27 groups. However, the exercise database of 232 patients is representative of HF populations in most tertiary referral clinical practices, and even with the smaller subgroups, the results are both statistically and clinically significant. Finally, we are cognizant that the inclusion of patients on β-blockers in the analysis might have limited the results. This did not turn out to be the case. The use of β-blockers in the Ile164 paired group was nearly identical to the Thr164 group. Furthermore, in the analysis of the invasive exercise testing of Ile164, no patients were taking β-blockers, and a significant difference was again observed in peak VO2. Also, there was no confounding for β-blocker usage in the analysis of the polymorphisms at 16 and 27, and the results were unchanged when patients taking β-blockers were excluded in the larger study with the polymorphisms at positions 16 and 27. Nevertheless, a prospective trial assessing whether β-blockers can modify these genetic influences is necessary to exclude this potential.

In conclusion, the Ile164 polymorphism of the fourth transmembrane-spanning domain negatively impacts exercise performance in patients with HF caused by idiopathic or ischemic cardiomyopathies. The presence of the heterozygous Ile164 receptor (regardless of the allele at position 16 and 27) is associated with the most depressed cardiac and vascular responses to exercise, even when accounting for other clinical parameters, such as NYHA FC, cause of HF, LVEF, or medication use. This is consistent with our recent report showing decreased survival in patients with Ile164.7 Taken together, then, these results point to the genotype of the β2AR at position 164 as being an important genetic component in the pathophysiology of HF. Patients with Gly16 or Gly16/Gln27 also exhibited decreased peak VO2 compared with the other genotypic combinations. On the basis of these findings and our in vitro and transgenic results, it appears that β2AR polymorphisms have a significant modifying effect in HF. β2AR genotyping may thus be a useful test in the clinical evaluation of patients with HF, providing a genetic basis for altering drug therapy or early listing for transplantation.

Acknowledgments

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References


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