Myocardial β-adrenoceptor down-regulation early after infarction is associated with long-term incidence of congestive heart failure

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Aims Adverse left ventricular (LV) remodelling after myocardial infarction (MI) frequently leads to congestive heart failure (CHF). We have previously shown that myocardial β-adrenoceptor density (β-ARD) is reduced soon after acute MI and correlates with LV dilatation in the short term. The aim of the present study was to determine whether myocardial β-ARD measured early after MI was associated with progression to CHF in the long term.

Methods and results We prospectively included 61 consecutive patients (mean age, 52 ± 11 years, 10 female) in whom MI was the first manifestation of coronary artery disease. Two to 4 weeks after MI, patients underwent positron emission tomography with S-[11C]CGP 12177 to measure β-ARD and 15O-labelled water to measure myocardial blood flow and coronary flow reserve. Patients were followed-up for a median of 12.7 years (interquartile range, 6.5–13.7 years) and incidence of CHF was recorded. Eleven patients (18%) developed CHF during follow-up. They had lower β-ARD compared with those who did not (5.35 vs. 6.49 pmol/g, P = 0.001). In patients with myocardial β-ARD ≤ 5.57 pmol/g, 10-year CHF incidence rates were higher than in patients with β-ARD > 5.57 pmol/g (57% vs. 9%, P = 0.001). In a Cox regression model, only whole-heart β-ARD [hazard ratio (HR) 0.29; 95% confidence interval (CI), 0.15–0.58, P = 0.001] and β-ARD in remote myocardium (HR 0.32; 95% CI, 0.16–0.61, P = 0.001) were significantly associated with the incidence of CHF at follow-up.

Conclusion Reduced myocardial β-ARD early after MI is associated with the incidence of CHF on long-term follow-up.

Keywords β-Adrenoceptor • S-[11C]CGP 12177 • Myocardial infarction • Congestive heart failure • Positron emission tomography • Prognosis

Introduction Congestive heart failure (CHF) is a growing public health problem which affects 10 million patients across Europe and more than 5 million in the USA.1,2 Coronary artery disease (CAD) is by far the most common cause of CHF and accounts for approximately 70% of cases.3,4 In most of these patients an acute myocardial infarction (AMI) precedes the development of CHF, often by several years. The ischaemic injury triggers a number of adaptive mechanisms leading to changes in size, geometry, and function of the left ventricle (LV). This process, known as LV remodelling, is usually slow and may remain clinically silent until symptoms of CHF develop.4

Activation of the sympathetic nervous system plays an important role in LV remodelling and CHF. Myocardial ischemia damages sympathetic nerve terminals5 and initiates sympatho-excitatory mechanisms which are both additive to and independent of those elicited by systolic dysfunction.6–8 Chronically increased noradrenaline levels induce down-regulation of β1-adrenoceptors and altered signal transduction. In their classic work, Bristow et al.9,10 demonstrated that noradrenaline concentration is increased in endomyocardial biopsies from failing human LV,
resulting in a reduction of myocardial β-adrenoceptors (β-AR), a hallmark of CHF. A previous study with positron emission tomography (PET) in patients with hypertrophic cardiomyopathy showed that β-AR down-regulation was associated with a reduced re-uptake of [11C]-hydroxyephedrine by neural terminals in the myocardium. This reduced re-uptake leads to a less efficient disposal of catecholamines from the synaptic cleft and contributes to myocardial β-AR down-regulation in hypertrophic cardiomyopathy.

Positron emission tomography with the non-selective β-AR antagonist S-[11C]CGP 12177 allows the non-invasive measurement of myocardial β-adrenoceptor density (β-ARD) in vivo. Using this technique, Merlet et al. have demonstrated myocardial β-AR down-regulation in patients with idiopathic dilated cardiomyopathy. In CAD patients, we have demonstrated that myocardial β-ARD is reduced in the subacute phase of AMI in the absence of heart failure and that this correlated with LV dilatation in the short term. We have now followed this cohort of CAD patients for over 10 years after the occurrence of AMI. In the present investigation, we sought to ascertain whether myocardial β-ARD, measured with PET within 1 month of AMI, was associated with the progression to symptomatic CHF in the long term.

**Methods**

**Patient population**

Between July 1994 and June 1997, we prospectively included 61 patients (age 52 ± 11 years, 10 female) with AMI. Exclusion criteria were any prior AMI or angina pectoris, significant CAD (defined as ≥50% diameter stenosis on coronary angiography) in arteries other than the infarct-related vessel, hypertension, diabetes, or renal failure. The study population is shared with a prior publication from this group. The study protocol was approved by the local Research Ethics Committee and all patients gave written informed consent. Radiation exposure was licensed by the UK Administration of Radioactive Substances Advisory Committee.

Medical treatment for AMI was left to the admitting physician and included thrombolysis in over 90% of the patients. Coronary angiography was performed in all patients within 10 days of their AMI followed by percutaneous coronary interventions (PCI) as deemed appropriate by the interventional cardiologist. Thrombolysis in myocardial infarction (TIMI) flow in the infarct-related artery was assessed before (baseline) and after PCI as previously described.

**Positron emission tomography image acquisition**

All patients underwent PET within 1 month of the AMI. Positron emission tomography image acquisition was performed on an ECAT 931-08/12 scanner (CTI/Siemens, Knoxville, TN, USA). The scan protocol consisted of a 20-min transmission scan, a blood pool scan with oxygen-15-labelled carbon monoxide ([15O]CO), two myocardial blood flow (MBF) scans with oxygen-15-labelled water ([15O]H2O) (at rest and during vasodilator stress with dipyridamole), and a myocardial β-ARD scan with S-[11C]CGP 12177. Details of the scan protocols and image reconstruction algorithms have been described extensively in prior reports.

**Positron emission tomography analysis and image processing**

After image reconstruction, normalization, and attenuation correction, PET images were resliced into a stack of short axis slices (slice thickness, 6.6 mm) encompassing the LV from the apex to the mitral annulus. Regions of interest (ROIs) were defined on short axis slices by dividing the LV myocardium according to the 16-segment model proposed by the American Heart Association. These myocardial tissue ROIs were then applied to all emission images of the different scans. The ROIs located in the territory subtended by the infarct-related artery were combined as ‘infarcted myocardium’ and those in remote territories (subtended by non-stenotic arteries) as ‘remote myocardium’.

**Measurement of myocardial blood flow**

Myocardial blood flow was calculated as previously reported and given in mL of blood per minute per gram of myocardium (mL/min/g). In brief, an arterial input function was obtained from a left atrial ROI on the [15O]CO emission scan. Thereafter, arterial input and myocardial tissue (obtained from myocardial tissue ROIs on [15O]H2O emission scans) time-activity curves were fitted to a single-compartment tracer kinetic model. Myocardial blood flow was corrected for partial volume effect and spillover of activity from the LV cavity. Coronary flow reserve (CFR) was calculated as the ratio of hyperaemic over resting MBF and provides an estimate of total coronary vasodilator reserve.

**Measurement of β-adrenoceptor density**

Positron emission tomography imaging for β-ARD was performed using a modified double-injection method as previously described. In brief, after correction for radioactive decay and vascular activity, the slow clearance sections of the myocardial tissue time-activity curves were extrapolated on the start of the infusions. β-ARD was calculated as the maximum number of available specific CGP binding sites per gram of tissue and corrected for partial volume using the perfusable tissue index. Hence, β-ARD is reported per gram of perfusable (i.e., viable) tissue.

**Echocardiography**

Echocardiography was performed within 1 month of AMI on the same day of the PET study using a Challenge 7000 echocardiograph (Esaote Biomedica, Florence, Italy). All echocardiograms were analysed by consensus of two experienced cardiologists who were blinded to clinical data and PET results. End-systolic volume (ESV) and end-diastolic volume (EDV) were measured using a single-plane area length method and ejection fraction (EF) calculated as 100 × (EDV − ESV)/EDV.

**Follow-up**

Follow-up data were obtained by a single observer (blinded to PET and echocardiography results) from hospital records or by telephone interviews of the general practitioner using a structured questionnaire. The primary endpoint was the development of CHF defined by the classic Framingham criteria, with two major or one major and two minor criteria required to diagnose CHF. Briefly, major criteria included paroxysmal nocturnal dyspnoea, neck vein distension, rales, radiographic cardiomegaly, pulmonary oedema, S3 gallop, increased central venous pressure, hepatojugular reflux, and weight loss in response to CHF treatment. Minor criteria included bilateral ankle oedema, nocturnal cough, dyspnoea on exertion, hepatomegaly, pleural effusion, decrease in vital capacity, and tachycardia. Secondary endpoints were all-cause mortality, recurrent myocardial infarction...
was performed with SPSS 16.0.1 (SPSS, Inc., Chicago, IL, USA). The patients’ baseline characteristics are listed in Table 1. All 61 patients completed the PET and echocardiography studies successfully. The patients’ baseline characteristics are listed in Table 1. None of the patients had overt CHF or was treated with beta-blockers at the time of the baseline PET and echocardiography scans. Baseline TIMI flow (before PCI but after thrombolysis) was 0 in 5 (8%) patients, 1 in 18 (30%) patients, 2 in 34 (56%) patients, and 3 in 4 (7%) patients. Thrombolysis in myocardial infarction flow after PCI was 0 in none, 1 in 2 (3%) patients, 2 in 8 (13%) patients, and 3 in 51 (84%) patients. None of the patients had signs of recurrent ischemia 1 month after AMI. There were no significant differences in peak creatine kinase (CK) levels, utilization of thrombolysis or PCI, TIMI flow at baseline and after PCI, infarct regions, and ancillary medical treatment between patients with CHF on follow-up vs. patients without.

### Myocardial blood flow

Average global MBF and CFR for the whole LV are shown in Table 2. No significant differences were observed between patients with CHF on follow-up vs. patients without. Resting and hyperaemic MBF were both lower in infarcted myocardial territories compared with remote (resting MBF, 0.87 ± 0.26 vs. 0.98 ± 0.28 mL/min/g, \( P = 0.01 \); hyperaemic MBF, 2.06 ± 1.05 vs. 2.57 ± 1.16, \( P < 0.001 \)). However, among patients with CHF on follow-up, MBF in both infarcted and remote territories did not differ from patients without CHF.

### β-Adrenoceptor density

Infarcted territories were characterized by a lower β-ARD compared with remote (\( P = 0.005 \) (Table 2). β-ARD in the whole heart and remote myocardium was significantly lower in patients who developed CHF on follow-up compared with those who did not, whereas no significant difference was observed for infarcted myocardium β-ARD. Whole-heart β-ARD did not correlate significantly with any of the following parameters: EF, LV

### Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical data were expressed in numbers and percentages. A paired or unpaired t test was used for comparison of means and a \( \chi^2 \) test or Fisher’s exact test for categorical data where appropriate. All tests were two-sided. Results from PET and echocardiography were correlated using Pearson’s method. Receiver operating characteristic curves (ROCs) were employed to determine the optimal cut-off for β-ARD to predict events on follow-up. Cumulative event rates over time were analysed with the Kaplan–Meier method and compared with the log-rank test. Univariate Cox regression analysis was used to determine variables that correlated with outcomes. Results from the Cox models are presented as hazard ratios (HRs) with their respective 95% confidence intervals (CIs). Statistical analysis was performed with SPSS 16.0.1 (SPSS, Inc., Chicago, IL, USA). A \( P \)-value <0.05 was considered statistically significant.

### Results

#### Study population

All 61 patients completed the PET and echocardiography studies successfully. The patients’ baseline characteristics are listed in Table 1. None of the patients had overt CHF or was treated with beta-blockers at the time of the baseline PET and echocardiography scans. Baseline TIMI flow (before PCI but after thrombolysis) was 0 in 5 (8%) patients, 1 in 18 (30%) patients, 2 in 34 (56%) patients, and 3 in 4 (7%) patients. Thrombolysis in myocardial infarction flow after PCI was 0 in none, 1 in 2 (3%) patients, 2 in 8 (13%) patients, and 3 in 51 (84%) patients. None of the patients had signs of recurrent ischemia 1 month after AMI. There were no significant differences in peak creatine kinase (CK) levels, utilization of thrombolysis or PCI, TIMI flow at baseline and after PCI, infarct regions, and ancillary medical treatment between patients with CHF on follow-up vs. patients without.

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 61)</th>
<th>CHF (n = 11)</th>
<th>No CHF (n = 50)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52 ± 11</td>
<td>55 ± 13</td>
<td>52 ± 11</td>
<td>0.39</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>10 (16)</td>
<td>2 (18)</td>
<td>8 (16)</td>
<td>&gt;0.99</td>
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<tr>
<td>Culprit artery, n (%)</td>
<td></td>
<td></td>
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<td>0.54</td>
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<tr>
<td>LAD</td>
<td>28 (46)</td>
<td>4 (36)</td>
<td>24 (48)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>6 (10)</td>
<td>2 (18)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>27 (44)</td>
<td>5 (45)</td>
<td>22 (44)</td>
<td></td>
</tr>
<tr>
<td>Peak CK levels, U/L</td>
<td>1704 ± 1482</td>
<td>1238 ± 541</td>
<td>1779 ± 1575</td>
<td>0.46</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>58 (95)</td>
<td>10 (91)</td>
<td>48 (96)</td>
<td>0.46</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>54 (89)</td>
<td>9 (82)</td>
<td>45 (90)</td>
<td>0.60</td>
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<tr>
<td>TIMI flow baseline</td>
<td>1.6 ± 0.7</td>
<td>1.7 ± 0.6</td>
<td>1.6 ± 0.8</td>
<td>0.55</td>
</tr>
<tr>
<td>TIMI flow post-PCI</td>
<td>2.8 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Medical treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASP</td>
<td>61 (100)</td>
<td>11 (100)</td>
<td>50 (100)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>30 (49)</td>
<td>4 (36)</td>
<td>26 (52)</td>
<td>0.51</td>
</tr>
<tr>
<td>CCB</td>
<td>34 (56)</td>
<td>8 (73)</td>
<td>26 (52)</td>
<td>0.38</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation unless otherwise indicated.

CHF, congestive heart failure; CK, creatine kinase; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; ASP, aspirin; ACE, angiotensin converting enzyme; CCB, calcium channel blockers.

*P* value for comparison between patients with CHF vs. those without CHF on follow-up.
Beta-Adrenoceptor density and heart failure incidence

**Table 2** Positron emission tomography and echocardiography results

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 61)</th>
<th>CHF (n = 11)</th>
<th>No CHF (n = 50)</th>
<th><strong>P</strong>(^{†})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global MBF and CFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Resting MBF, mL/min/g</td>
<td>0.91 ± 0.19</td>
<td>0.94 ± 0.34</td>
<td>0.90 ± 0.15</td>
<td>0.55</td>
</tr>
<tr>
<td>Hyperaemic MBF, mL/min/g</td>
<td>2.26 ± 0.91</td>
<td>2.14 ± 1.21</td>
<td>2.29 ± 0.85</td>
<td>0.63</td>
</tr>
<tr>
<td>CFR</td>
<td>2.47 ± 0.83</td>
<td>2.25 ± 0.85</td>
<td>2.52 ± 0.83</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Beta-Adrenoceptor density</strong></td>
<td></td>
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<tr>
<td>Whole LV, pmol/g</td>
<td>6.29 ± 0.98</td>
<td>5.35 ± 0.80</td>
<td>6.49 ± 0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infarcted myocardium, pmol/g</td>
<td>6.22 ± 1.34(^{†})</td>
<td>5.77 ± 1.86</td>
<td>6.32 ± 1.19</td>
<td>0.23</td>
</tr>
<tr>
<td>Remote myocardium, pmol/g</td>
<td>6.70 ± 1.17</td>
<td>5.54 ± 0.79</td>
<td>6.96 ± 1.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ESV, mL</td>
<td>63 ± 22</td>
<td>70 ± 29</td>
<td>61 ± 20</td>
<td>0.21</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>118 ± 34</td>
<td>129 ± 47</td>
<td>116 ± 31</td>
<td>0.24</td>
</tr>
<tr>
<td>EF, %</td>
<td>47 ± 8</td>
<td>46 ± 6</td>
<td>48 ± 8</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.
MBF, myocardial blood flow; CFR, coronary flow reserve; LV, left ventricle; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction.
\(^{†}\)P = 0.005 for comparison with remote myocardium.
\(^{†}\)P-value for comparison between patients with CHF vs. those without CHF at follow-up.

LV volumes, resting and hyperaemic MBF, TIMI flow at baseline and after PCI, and peak CK levels.

**Echocardiographic findings**

LV volumes and EF at baseline were similar in patients who developed CHF on follow-up compared with those who did not. Average EF in the study population was 47 ± 8% (range, 32–68%) with 24 (39%) patients having an EF below 45% (Table 2).

**Follow-up data**

Thirteen (21%) patients were lost to follow-up immediately after conclusion of the initial short-term study,\(^{13}\) and were therefore censored after 6 months in the survival analysis. On follow-up, 11 (18%) patients developed CHF after a median of 4.6 years (range, 0.5–11.0 years). Receiver operating curve analysis demonstrated a good diagnostic accuracy of whole-heart \(\beta\)-ARD to detect CHF on follow-up (area under the curve, 0.83; 95% CI, 0.71–0.92) and yielded an ideal discriminatory cut-off at 5.57 pmol/g (sensitivity, 73%; specificity, 88%). Figure 1 shows the Kaplan–Meier curves for survival free of CHF in patients with lower (\(\leq 5.57\) pmol/g, \(n = 14\)) myocardial \(\beta\)-ARD compared with those with higher \(\beta\)-ARD (\(>5.57\) pmol/g, \(n = 47\)). Ten-year CHF incidence rates were higher in patients with lower \(\beta\)-ARD compared with those with higher \(\beta\)-ARD (57% vs. 9%, \(P < 0.001\)) (Figure 2A) and the effect was preserved across the two strata of EF (\(P\) for interaction = 0.46) (Figure 2B). Patients with lower \(\beta\)-ARD also had significantly higher rates of the composite endpoint, but no differences were noted for other secondary endpoints (Table 3).

Cox regression analysis showed that only \(\beta\)-ARD in remote myocardium and the entire LV were associated with CHF development at follow-up (Figure 3) of which whole-heart \(\beta\)-ARD showed the strongest association (HR 0.29; 95% CI, 0.15–0.58; \(P < 0.001\)). Cox analysis for secondary endpoints revealed a significant association of TIMI flow after PCI (HR 0.26, 0.10–0.67; \(P = 0.005\)), and hyperaemic MBF (HR 0.31, 0.12–0.84; \(P = 0.02\)) with total mortality. Age was significantly associated with the incidence of stroke (HR 1.17, 1.03–1.33; \(P = 0.01\)).

**Discussion**

Our findings demonstrate that myocardial \(\beta\)-ARD measured with PET within 1 month of AMI in patients with relatively well preserved EF is strongly associated with the incidence of CHF on long-term follow-up. Reduction in \(\beta\)-ARD by 1 pmol/g translates into a three-fold increased risk of developing CHF over the ensuing 10 years. Notably, in our patients, only \(\beta\)-ARD was significantly associated with CHF at long-term follow-up. This underscores...
the pathophysiological importance of sympathetic nervous system activation in LV remodelling and CHF after AMI.

Interestingly, in our study population, neither age nor LV–EF measured at baseline was associated with the development of CHF on follow-up. This finding may seem surprising given the abundant body of evidence demonstrating an important prognostic role of these two clinical parameters in the aftermath of AMI. Nonetheless, our study population consisted of AMI survivors of young age with relatively preserved LV–EF, a subgroup in which both parameters have been demonstrated to have little impact on the prognostication of CHF. In these patients, the LV remodelling process may be more subtle and protracted over a longer period of time (and therefore not evident 1 month after AMI), but appears to be preceded by an increased cardiac sympathetic activity and reduced β-ARD.

On the other hand, global hyperaemic MBF (i.e. the average of territories subtended by diseased and non-diseased epicardial coronary arteries) was significantly associated with total mortality, underlining the important prognostic role of microvascular function in patients with AMI which has been previously demonstrated. This finding is in keeping with prior reports documenting an important association of global hyperaemic MBF with mortality in patients at risk of cardiovascular events and in more selected populations with hypertrophic or dilated cardiomyopathy.

The role of the sympathetic nervous system in left ventricular dysfunction

The heart of patients with chronic LV dysfunction is characterized by a significant reduction of pre-synaptic noradrenaline re-uptake and post-synaptic β-ARD. In experimental preparations, noradrenaline has a direct toxic effect on feline adult myocytes grown in cell culture that is attenuated by β-AR blockade and mimicked by selective stimulation of the β-AR, suggesting that chronic cardiac sympathetic nervous activation following MI may cause progressive direct damage to the myocytes, leading to LV remodelling and overt heart failure.

The increased sympathetic activity in the failing LV is a global rather than a regional phenomenon, limited to the infarct or peri-infarct zone, which contributes to the remodelling process of the whole LV. Complex changes in the regulatory homeostasis of the cardiovascular system sustain the hyperactivity of the sympathetic nervous system observed in the failing heart, where the final result is a balance between mechanisms compensating for impaired systolic function and unrestrained excitatory stimuli that unduly increase adrenergic responses. Different radiotracers labelled with positron or single-photon emitters have been developed to

![Figure 2](image-url)
probe both pre-synaptic noradrenaline re-uptake and post-synaptic β-ARD.29,30

Imaging cardiac sympathetic activity and its potential clinical value

Measurement of regional activity of the sympathetic nervous system has been hampered by the inaccessibility to testing the sympathetic endings in the heart. The non-selective β-AR antagonist CGP 12177 labelled with 11C ([11C]CGP 12177, half life 20 min) is a suitable ligand for the measurement of total myocardial β-ARD since it has a high affinity, is hydrophilic (i.e. it does not cross the cell membrane), and therefore binds only to the functionally active cell surface receptors.16,31 Myocardial β-ARD measured with PET and S-[11C]CGP 12177 is reduced in patients with heart failure due to dilated cardiomyopathy, and down-regulation of myocardial β-AR is more pronounced in patients with hypertrophic cardiomyopathy who proceed to LV dilatation and CHF.12,31 In our previous study in patients with CAD we have shown that the degree of down-regulation of myocardial β-AR in the subacute phase of AMI correlates with progressive LV chamber dilatation over the following 6 months.13 The present data extend these original observations by adding follow-up information and demonstrating a higher risk for developing CHF in patients with more severely reduced myocardial β-ARD. Asymptomatic patients with relatively preserved EF, such as those of our study, do not usually receive long-term treatment with beta-blocking agents. Thus, a reduced myocardial β-ARD might identify a subgroup of patients in whom long-term treatment with beta-blocking agents is warranted.

More recently radioactive tracers have become available for probing pre-synaptic noradrenaline re-uptake.123I-metaiodobenzylguanidine (MIBG) is the most widely used in combination with single-photon emission computed tomography (SPECT). Impaired MIBG uptake, revealed by a low late heart-to-mediastinum ratio, is strongly and independently related to mortality in patients with heart failure independently of its cause.32,33 In a number of recent studies, among all clinical and imaging variables, only the reduction of late heart to mediastinum ratio and LV-EF were independent predictors of mortality, with late heart-to-mediastinum ratio being the best predictor of event-free survival.34,35 In the near future, the results of the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) trial will provide prospective validation of the potential role of the evaluation of regional sympathetic activity by means of MIBG SPECT in assessing prognosis and developing management strategies for patients with CHF.36 None of the MIBG studies published so far, however, has addressed the issue of predicting CHF development after AMI in patients with relatively preserved EF.

Study limitations

We acknowledge a limited number of study participants and the number of patients who developed HF is small. The limited number of patients and events precluded the use of large multivariate models and restricted the number of covariates entered in the model to assess independent prognostic effects. Our findings should be validated in subsequent studies with larger cohorts of patients.

The production of S-[11C]CGP 12177 is laborious and requires a cyclotron on site and blood sampling analysis for the quantification of β-ARD which is clearly a limitation for a wide clinical application of this tracer. The PET tracer S-[11C]CGP 12388 has comparable biological characteristics to S-[11C]CGP 12177, but can be obtained through a simpler radiochemical method.37 Alternative longer lived or single-photon emitting radioligands for probing cardiac sympathetic function should be tested for patient stratification soon after AMI.

Figure 3 Univariate Cox proportional hazard model for prediction of congestive heart failure (CHF) events. A significant inverse relationship between myocardial β-ARD (remote and whole heart) and the hazard rates of CHF can be noted. TIMI, thrombolysis in myocardial infarction blood flow; PCI, percutaneous coronary intervention; MBF, myocardial blood flow; CFR, coronary flow reserve; β-ARD, β-adrenoceptor density; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (0.98–1.08)</td>
<td>0.30</td>
</tr>
<tr>
<td>TIMI baseline</td>
<td>1.19 (0.49–2.91)</td>
<td>0.70</td>
</tr>
<tr>
<td>TIMI post PCI</td>
<td>0.49 (0.17–1.41)</td>
<td>0.19</td>
</tr>
<tr>
<td>MBF at rest</td>
<td>1.25 (0.05–30.39)</td>
<td>0.89</td>
</tr>
<tr>
<td>MBF at stress</td>
<td>0.71 (0.33–1.53)</td>
<td>0.38</td>
</tr>
<tr>
<td>CFR</td>
<td>0.59 (0.25–1.42)</td>
<td>0.24</td>
</tr>
<tr>
<td>β-ARD Infarct</td>
<td>0.69 (0.43–1.12)</td>
<td>0.13</td>
</tr>
<tr>
<td>β-ARD Remote</td>
<td>0.32 (0.16–0.61)</td>
<td>0.001</td>
</tr>
<tr>
<td>β-ARD Whole heart</td>
<td>0.29 (0.15–0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESV</td>
<td>1.02 (0.99–1.04)</td>
<td>0.19</td>
</tr>
<tr>
<td>EDV</td>
<td>1.01 (0.99–1.03)</td>
<td>0.22</td>
</tr>
<tr>
<td>EF</td>
<td>0.97 (0.89–1.05)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Clinical implications

In summary, a reduced myocardial β-ARD measured by PET with [11C]CGP 12177 in asymptomatic patients with relatively preserved EF within 1 month of AMI was associated with an increased risk of developing CHF on long-term follow-up. This technique could provide a closer insight into the β-AR down-regulation and its reversibility with therapy. Additionally, our results, if confirmed by larger scale trials, could provide a rationale for post AMI treatment with β-AR antagonists in patients with reduced β-ARD, even if LV function is relatively preserved.

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References


