The association between cardiac events and myocardial ischaemia following thrombolysis in acute myocardial infarction and the impact of carvedilol

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The majority of post-myocardial infarction studies with \( \beta \)-blocking drugs involved earlier generations. Newer drugs of this family with additional vasodilating and free-radical suppression properties, such as carvedilol, are now available which may improve the prognosis still further. This double-blind, randomized, placebo-controlled, parallel group study was designed to assess the extent of myocardial ischaemia in clinically stable patients 6 weeks after acute myocardial infarction and thrombolysis, and to determine the influence of carvedilol on ischaemic events during the subsequent 6 months. One hundred and one patients who remained event free at 6 weeks post myocardial infarction underwent rest and exercise thallium-201 (Tl-201) imaging. Reversible ischaemia was detected in 70 of the patients and there were 13 events in this group compared to one event in the 31 patients without ischaemia \((P=0.07)\). Four of the 56 patients on carvedilol and 10 of the 45 on placebo had adverse cardiac events \((P=0.04)\). In patients with reversible ischaemia carvedilol was more effective in reducing these events than was placebo \((P=0.03)\). These studies demonstrate that reversible myocardial ischaemia detected by Tl-201 imaging is present in a large proportion of clinically stable patients following thrombolysis. In these patients, there is an increased cardiac event rate which is significantly reduced by carvedilol.

\textbf{Key Words:} Acute myocardial infarction, thallium imaging, prognosis, carvedilol.

\section*{Introduction}

Thrombolysis after acute myocardial infarction reduces mortality risk but frequently leaves areas of ischaemic myocardium, which may subsequently generate further cardiac events\(^{[1-3]}\). However, the latter may be overcome by early treatment with \( \beta \)-blocking drugs, which reduce ischaemic events and mortality risk. Administered intravenously these drugs resulted in a 13% reduction of early mortality when used within 24 h of chest pain\(^{[4,6]}\), and when used as long-term treatment, they also reduce the risks of reinfarction and death\(^{[7]}\). However, all these studies were conducted prior to the use of thrombolysis and aspirin and the safety and efficacy of \( \beta \)-blocking drugs in the setting of current clinical practice is unclear. The results of a recent study highlighted the potential hazard of intravenous beta-blockade following thrombolysis for acute myocardial infarction\(^{[9]}\).

Carvedilol is a non-selective \( \beta \)-adrenoceptor antagonist with additional vasodilating properties due to \( \alpha \)-1 adrenoceptor blockade\(^{[10]}\). Previous studies have shown that it is efficacious in angina\(^{[11]}\), hypertension\(^{[12]}\) and in patients with left ventricular dysfunction\(^{[13,14]}\). Additionally, it has no adverse effects on plasma lipid concentrations\(^{[15]}\), is safe in partially nephrectomized animals\(^{[16]}\) and limits experimental myocardial infarction size\(^{[17]}\). Carvedilol has also been shown to possess anti-oxidant properties which endow it with the potential to attenuate myocardial damage due to free radical release\(^{[18]}\). Thus, from a theoretical viewpoint, carvedilol has a suitable pharmacological profile for the management of acute myocardial infarction, without the potential hazard of inducing heart failure.

Thallium-201 myocardial perfusion imaging has been widely utilized for assessing the severity and extent of reversible myocardial ischaemia. The prognostic value of Tl-201 imaging following acute myocardial infarction, and its ability to define high and low risk groups on the basis of presence or absence of ischaemia is well documented\(^{[19-21]}\).

The present study was designed with three objectives. First, to assess the incidence and extent of myocardial ischaemia by Tl-201 imaging at 6 weeks in myocardial infarction survivors who had undergone thrombolysis. Second, to determine the influence of the presence or absence of myocardial ischaemia on subsequent cardiac events. Third, to measure the effects of treatment with carvedilol on adverse cardiac events in

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these patients. This study was incorporated in the protocol of the Carvedilol Heart Attack Pilot Study (CHAPS)[22].

Patients and methods

Patient selection and inclusion

Patients admitted to a coronary care unit within 24 h of the onset of symptoms of acute myocardial infarction, with consistent electrocardiographic changes, and elevated serum creatine kinase and the membrane-bound fraction of creatine kinase were recruited to the study with their informed consent. Patients in whom myocardial infarction was not confirmed by subsequent elevation of cardiac enzymes were later withdrawn.

Exclusions included patients already on $\alpha$ or $\beta$-blocking drugs or calcium antagonists, those with contraindications to these drugs, those in cardiogenic shock or with severe bradycardia, hypotension, second- or third-degree heart block, left bundle branch block, valvular heart disease, insulin dependent diabetes, renal failure (creatinine $>$ 159 $\mu$mol l$^{-1}$), known malignancy or other severe disease and pregnancy.

One hundred and fifty-one patients were recruited into the trial of whom 147 had undergone thrombolysis. All were randomized to placebo or carvedilol at the time of hospital admission. Forty three were subsequently withdrawn as unconfirmed AMI or other severe disease and pregnancy. The 101 patients included 89 male and 12 female patients with an age range of 34–81 (mean 61) years. Fifty-five were current or previous smokers, 15 had a history of coronary artery disease, 15 were hypertensive and 13 diabetic. There were 52 anterior (including septal and lateral) and 49 inferior (including posterior) myocardial infarctions. All 101 patients had presented within 24 h of onset of chest pain, all had been thrombolyzed, and their mean peak creatinine kinase level was 1767 i.u.

Study design

The study was a double-blind, randomized, parallel-group comparison of carvedilol and placebo with stratifications for anterior or inferior location of myocardial infarction and for thrombolysis or no thrombolysis. End points were defined as cardiac death, reinfarction, unstable angina, heart failure, emergency coronary revascularization, ventricular arrhythmias requiring intervention, cerebro-vascular accident and additional cardiovascular drug therapy other than sublingual nitrates for angina. Initiation of ACE inhibitors, digitalis or anti-arrhythmic drugs during the study was also considered an end-point.

Drug therapy

All patients were given aspirin, subcutaneous heparin for 3 days and thrombolysis on admission to the coronary care unit. Following informed consent, patients were given intravenous carvedilol 2.5 mg or placebo over 15 min followed after 4 h by oral carvedilol 6.25 mg or matching placebo and then 6.25 mg b.d. for 2 days. Carvedilol was then increased to 12.5 mg twice daily and maintained at 12.5 mg to 25 mg b.d. for the remainder of the 6 months or until a cardiovascular end-point. Dose titration was performed at day 14, with carvedilol being increased to 25 mg b.d. if blood pressure was $>$ 120/95 and heart rate $>$ 55 beats min$^{-1}$. The dose of carvedilol was also increased if the patient developed angina.

Exercise and rest TI-201 scintigraphy

Patients underwent a symptom-limited exercise test using the Bruce protocol, at 6 weeks post infarction on a motorized treadmill with continuous computer averaged electrocardiographic signal analysis (CASE 12, Marquette Electronics, Milwaukee, U.S.A.). Standard end-points were monitored for test termination.

At peak exercise, 74 Mbq of TI-201 was injected intravenously and patients continued to exercise for a further minute. Images were acquired by a mobile gamma camera (Elscint, 205M) attached to a low energy all-purpose collimator with an energy window setting of 68–83 KeV. Planar images were obtained following injection of TI-201, in the anterior, 45% left anterior oblique and left lateral views. Imaging was performed for 10 min per view. A rest study was performed within 5 days of the exercise study; TI-201 was injected 10 min after pre-treatment with sublingual nitroglycerine (0.5 mg) and imaging performed 60 min later. Correct angulation was obtained for each image and patient positioning strictly controlled as previously described[23].

Image analysis

TI-201 images were analysed semi-quantitatively by two independent observers blinded to patient identity and clinical diagnosis. Differences in interpretation were resolved by consensus. Five myocardial regions were defined from the three planar views and this was converted to a polar map with four segments in each of the following regions: anterior, lateral, inferior and septal regions with two segments forming the apex[24,25].
Planar images were assessed semi-quantitatively using both unenhanced images on a computer grey scale as well as processed images with smoothing and colour coding. Matching views from initial uptake, and separate day rest study were displayed side by side for comparison. The TI-201 activity in each segment was graded as normal, mildly reduced, moderately reduced, severely reduced or absent using a 5-point score (1=normal uptake, 5=absent). The initial scan was considered normal if all 18 segments had normal regional myocardial perfusion. Reversible defect in a segment was considered to be present when there was a shift towards normal of at least two grades or complete normalization of the rest image compared with the exercise image. Patients were categorized on the basis of the presence or absence of at least two partially or fully reversible segments from the exercise stress to the subsequent rest TI-201 image. Fully or partially reversible scans were considered to be indicative of myocardial ischaemia induced by the treadmill exercise.

**Statistical analysis**

Logistic regression analysis was used to predict whether or not any of the 101 patients experienced a cardiovascular event during the subsequent 6 month follow-up period. The effects on cardiac events of two variables were considered: (a) treatment with carvedilol or placebo, (b) the presence or absence or reversible perfusion defects on TI-201 imaging. Logistic regression analysis was performed separately for each variable and then using both variables together.

**Results**

**Safety profile**

Administration of carvedilol (intravenous or oral) was not associated with any serious adverse effects. A greater number of patients dropped out of the placebo group than out of the group taking carvedilol due to cardiac events. There were four withdrawals in the carvedilol group and three in the placebo group due to non-cardiac adverse events.

**Adverse cardiac events**

Fourteen cardiovascular events occurred during the 6 month follow-up (Table 1; Fig. 1). TI-201 imaging demonstrated reversible perfusion abnormalities in 70 patients, while 31 had no evidence of reversible perfusion defects. In the 70 patients who had reversible perfusion defects, there were 13 cardiac events compared with only one event amongst the 31 patients with non-reversible perfusion defects (hazard ratio 6.8; 95% confidence interval 0.85-54.8; P=0.07 (Fig. 2). Four cardiac events occurred amongst the 56 patients on carvedilol and 10 events amongst the 45 patients on placebo (hazard ratio 0.27; 95% confidence interval=0.08-0.93; P=0.04) (Figs 3 and 4).

**Table 1 Numbers of patients and events on carvedilol (C) and placebo (P); with or without reversible myocardial ischaemia**

<table>
<thead>
<tr>
<th></th>
<th>C Events</th>
<th>P Events</th>
<th>Total Events</th>
</tr>
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<tbody>
<tr>
<td>Ischaemia present</td>
<td>39</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Ischaemia absent</td>
<td>17</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>4</td>
<td>45</td>
</tr>
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Effect of treatment on cardiac events P=0.04; presence or absence of ischaemia on cardiac events P=0.07, ns.

**Figure 1** Adverse cardiac events in all patients during the 6 month follow-up. Re-inf = re-infarction; CHF = congestive heart failure; UA = unstable angina; VT = ventricular tachycardia; PCTA = percutaneous angioplasty.

**Figure 2** Percentage of patients with and without reversible myocardial ischaemia in the carvedilol and placebo groups and the incidence of events (M). Hazard ratio: 0.27, 95% CI, 0.08-0.93, P=0.04, between carvedilol and placebo.
Reversible ischaemia detected by Tl-201 imaging. The difference was not statistically significant (P=0.07).

Figure 3

The incidence of adverse cardiac events related to the presence or absence of reversible myocardial ischaemia in the placebo and carvedilol treated groups (P=0.04).

Figure 4

Logistic regression analysis using both variables together to allow for interaction demonstrated that the effect of carvedilol in reducing adverse events in patients with reversible ischaemia was statistically significant (hazard ratio 0.25; 95% confidence intervals 0.07–0.89; P=0.03). However, the effect of the presence or absence of ischaemia on subsequent events, even allowing for the effect of the drug or placebo failed to reach statistical significance (hazard ratio 7.4; 95% confidence interval 0.9–60.7; P=0.06).

Discussion

★★-blockers have been shown to reduce chest pain, decrease infarction size and reduce both morbidity and mortality risks in acute and longer term trials. However, these studies were performed prior to the advent of thrombolysis and aspirin, which have greatly reduced mortality following infarction. Although thrombolysis reduces mortality, the salvaged myocardium remains at increased risk of further ischaemic events and the effects of β-blockade on this risk is unknown. The TIMI-IIIB study demonstrated no difference in 6 day mortality between the intravenous and oral metoprolol groups, but did show a reduction in ischaemic events with early intravenous β-blockade.

However, in the GUSTO trial, intravenous atenolol was associated with an increased incidence of circulatory shock, congestive heart failure, myocardial ischaemia and requirement for cardiac pacing.

Following successful thrombolysis, patients have a combined risk from further ischaemic events and the development of heart failure. Carvedilol has many pharmacodynamic attributes which may be advantageous in this situation. It has also been shown to improve abnormal wall motion and improves myocardial salvage. Carvedilol may be of value in ischaemic heart failure, a situation where some β-blockers have failed to show efficacy.

Tl-201 imaging has been shown to be a valid technique for risk stratification following acute myocardial infarction, the presence of reversible perfusion defects being associated with an increased incidence of adverse cardiac events. This study utilized Tl-201 imaging to detect patients with reversible ischaemia, to assess the risk associated with such pathophysiology and to evaluate the role of carvedilol in modifying these risks. Tl-201 imaging revealed a large proportion of patients had exercise induced myocardial ischaemia despite the fact that they were clinically 'stable' at 6 weeks post infarction. Furthermore, one in five of these patients who demonstrated reversible myocardial ischaemia had an adverse cardiac event during the following 6 months; in contrast far fewer of the patients who did not have reversible myocardial ischaemia suffered an adverse cardiac event. Despite the relatively small number of thrombolysed patients studied, treatment with carvedilol was associated with a substantial reduction in adverse cardiac events (7%) compared to the incidence in patients given placebo (22%) (P=0.04). Furthermore, when these data were adjusted to take into account the presence or absence of reversible ischaemia, carvedilol treatment showed an increased benefit compared to placebo in those patients with reversible ischaemia (P=0.03). These results clearly demonstrate the anti-ischaemic and protective actions of carvedilol in this cohort of thrombolysed post-infarction patients.

In summary, these results show that a large proportion of patients who are clinically stable following acute myocardial infarction and thrombolysis have exercise induced myocardial ischaemia. Carvedilol significantly reduces the increased risk of cardiac events in these patients and improves their prognosis. This preliminary study furnishes grounds for the further evaluation of the role of carvedilol in reducing the
morbidty and mortality of patients following acute myocardial infarction.

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