New-onset angina preceding acute myocardial infarction is associated with improved contractile recovery after thrombolysis

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Background Ischaemic preconditioning reduces myocardial infarct size in animal models. Clinical data suggest that episodes of angina immediately before acute myocardial infarction may be associated with smaller infarct size in man. However, it is unclear whether ischaemic episodes preceding acute myocardial infarction also affect contractile recovery in patients.

Objective In this study we investigated the recovery of regional myocardial function after thrombolysis in two groups of patients at their first Q-wave acute myocardial infarction; in one group (n=42) myocardial infarction occurred unheralded, whereas patients of the second group (n=48) had experienced new-onset angina in the 48h that preceded infarction. Echocardiographic analysis of myocardial regional function in the infarct area was done at 2, 24 and 72h after thrombolysis, and at 1 week, and 1 and 3 months follow-up.

Results Peak level of Mb-creatine kinase was significantly lower in patients with new-onset angina (96 ± 47 as compared with 221 ± 108 IU.l⁻¹, P <0·01), as was the area under the Mb-creatine kinase curve (1321 ± 876 as compared to 3879 ± 1555 U.l⁻¹.36 h, P <0·01). Hypokinetic segments were fewer in patients with pre-infarction angina. Similarly, wall motion score improved significantly earlier in patients who had new-onset angina before acute myocardial infarction. Thus, contractile recovery was more rapid in patients with previous angina than in those in whom infarction occurred unheralded. Complications during the in-hospital outcome and other variables considered during the 4-week follow-up were similar between groups.

Conclusions Patients who experienced new-onset angina before acute myocardial infarction showed better recovery of regional function after thrombolysis. Our study supports the hypothesis that brief periods of ischaemia immediately before myocardial infarction may precondition the human heart, thus improving contractile recovery (Eur Heart J 1998; 19: 411–419)

Key Words: Preconditioning, stunning, regional function, coronary heart disease.

Introduction

Ischaemic preconditioning is the phenomenon by which a brief episode of myocardial ischaemia increases the ability of the heart to tolerate a subsequent prolonged ischaemic injury[1,2]. Experimental studies showed that ischaemic preconditioning may reduce myocardial infarct size and/or improve post-ischaemic electrical and contractile dysfunction[1,2].

It also seems likely that human myocardium may be preconditioned[3,4]. One clinical condition that may reproduce the experimental model of ischaemic preconditioning is pre-infarction angina.

In a recent large study[5], the retrospective analysis of patients enrolled in the TIMI 4 trial has shown that previous episodes of angina resulted in a lower incidence of in-hospital death, severe heart failure or shock, and smaller infarct size. Importantly, this protection occurred despite multivessel coronary heart disease in the angina group and it was not dependent on angiographically visible epicardial coronary collateral blood vessels or on differences in use of antianginal
medication. Furthermore, other studies\[6\textendash}8\] support the idea that pre-infarction angina may act as a preconditioning stimulus.

In spite of these observations suggesting a preconditioning effect toward infarct size, the specific role of previous angina on the recovery of myocardial function after myocardial infarction is poorly investigated. Accordingly, the goal of the present study was to analyze the recovery of regional myocardial contractile function in patients after thrombolysis in whom myocardial infarction occurred unheralded, in comparison with patients who had new-onset angina within 48 h before their first myocardial infarction.

**Methods**

**Patients**

We studied, retrospectively, 42 consecutive patients who had had no episodes of angina before suffering an acute myocardial infarction, and compared them to 48 consecutive patients who had developed new-onset angina within 48 h before their first Q-wave myocardial infarction (this selection was done to include only patients who did not have sufficient time to develop new collaterals and without previous infarction wall motion abnormalities). Inclusion criteria included all patients less than 65 years old who had undergone thrombolysis, and in whom standard 12-lead ECGs showed ST-segment elevation of at least 0·1 mV in two precordial contiguous leads, suggesting anterior localization of infarction\[9\]. Patients were excluded if myocardial infarction was associated with left bundle branch block, valvular heart disease, severe hypertension, cardiac operation, or previous cerebral vascular accident. For the echocardiographic analysis, exclusion criteria were extended to patients with a poor acoustic window. Patients with chronic atrial fibrillation or intraventricular conduction defects were also excluded from the study. Physicians collected a detailed clinical history in all studied patients. However, we underline that new-onset angina is often a subjective parameter which renders it difficult to be measured accurately. Family history was considered positive when symptomatic coronary heart disease occurred in siblings, parents, parents’ siblings, or grandparents. Other variables considered were: information on the administration of certain therapies affecting myocardial function (beta-blockers, calcium antagonists, angiotensin converting enzyme-inhibitors, and nitrates), history of diabetes mellitus, dyslipidaemias (cholesterolemia \( \geq 200 \text{ mg} \cdot \text{dl}^{-1} \) and/or triglyceridaemia \( \geq 200 \text{ mg} \cdot \text{dl}^{-1} \), sedentary life style and smoking habits.

**Study design**

Echocardiographic evaluation of recovery of myocardial regional function was carried out 2, 24 and 72 h from the end of thrombolysis, and after 1 week, and 1 and 3 months. All patients discontinued drug therapy (all treatments) for 48 h before the day of examination at 1 and 3 months. Electrocardiographic variables and infarct size determined by creatine kinase release were also estimated. In-hospital events recorded in the coronary unit were: cardiac arrest, ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrioventricular blocks, congestive heart failure (presence of rales that do not clear with coughing over more than half the lung fields and X-ray confirmation of pulmonary congestion), reinfarction, recurrent ischaemic pain, and death. Finally, a 4-week follow-up of both groups of patients was performed that evaluated the following parameters: 4-week mortality, reinfarction, heart failure, unstable angina, coronary arteriography, and treatment with percutaneous transluminal coronary angioplasty. We recorded these data only to relate possible differences in echocardiographic parameters to visible disparity in the incidence of complications during the in-hospital outcome and the 4-week follow-up.

**Electrocardiographic measurements**

The 12-lead ECGs recorded the number of leads showing ST-elevation, the sum of ST-elevation above the baseline (SST of precordial leads \( V_1\textendash}V_6 \)), and the sum of R wave height in precordial leads \( V_1\textendash}V_6 \) (S.R)\[10\]. The following electrocardiographic variables were determined: presence or absence of ventricular tachycardia and fibrillation, atrial arrhythmias, and atrioventricular blocks.

**Thrombolysis**

Thrombolytic therapy was started with human-recombinant tissue-type plasminogen activator (alteplase) (60 mg i.v. over the first hour, with 10 mg being administered as an initial bolus twice at 20 min intervals followed by 40 mg as a continuous infusion within 1 h, and 40 mg i.v. during the subsequent 1·5 h; total dose, 100 mg) within 2·5 h of the onset of acute myocardial infarction. Immediately before administration of the thrombolytic agent, aspirin (200 mg) was given, and then was continued on a daily basis (100 mg . day\(^{-1}\)). A 5000 IU bolus of heparin was given just prior to thrombolysis, followed by additional heparin during the first 24 h, adjusted every 6 h to maintain the activated partial thromboplastin time between 2 and 2·5 times the control value. Efficacy of thrombolysis was defined by the following criteria: continuous ST-segment monitoring\[11\], early M B-creatine kinase peak (<18 h), sudden decrease in chest pain, and serial changes in abnormal wall motion. Time to reperfusion was measured blindly with regard to the history of preceding angina. Myocardial perfusion was believed to occur when ST-segment elevation decreased more than 60% relative to the most abnormal peak detected.
Venous blood samples were obtained every 4 h during the first 24 h after admission to the coronary care unit, and were used to measure total creatine kinase and its MB-isoenzyme. The upper limits of the normal range in our laboratory were 150 and 12·5IU.l for plasma creatine kinase and MB-isoenzyme, respectively. Creatine kinase and MB-isoenzyme values were then evaluated every 12 h until 96 h. The time to creatine kinase peak was measured from the onset of myocardial infarction symptoms. Infarct size was estimated by the method of Grande et al.[12] using the peak MB-creatine kinase values and the area under the curve of various concentrations as a function of time.

Echocardiographic analysis

Two-dimensional echocardiographic measurements were performed according to recommendations of the American Society of Echocardiography[13]. Images were recorded simultaneously with electrocardiographic tracings on magnetic videotapes. Left ventricular wall motion was evaluated by left ventricular end-diastolic and end-systolic silhouettes, as described[14]. The end-diastolic image was defined as the frame closest to the beginning of the Q-wave in lead II of the ECG. The end-systolic image was defined as the frame with the smallest left ventricular cavity (usually 10 to 12 frames past end-diastole, or 330 to 350 ms later). The degree of hypokinesis was then scored on a 5-point scale (0 = normal, 1 = mild hypokinetic, 2 = moderate hypokinetic, 3 = severe hypokinetic, 4 = akinetic). In addition, semi-quantitative analysis was performed on the parasternal short-axis images at the mid-papillary muscle level, as previously described in detail[14]. Briefly, from the centre of the left ventricle, 24 equally spaced segments were drawn to intersect the endocardial outlines for end-diastolic and end-systolic images. The contours in the freeze-frame image were then digitized by a sonic pen interfaced to a computed-assisted system (Hewlett-Packard). All segments that showed an inward motion depressed below the normal range in healthy subjects used as controls were taken to be hypokinetic. In the evaluation of both wall-motion and number of hypokinetic segments, repeated measurements were recorded in order to minimize the impact of movements of the heart during the cardiac cycle, respiratory movements or postural changes.

Statistical analysis

Data were analysed in a blinded-fashion with respect to knowledge of presence or not of angina. All results are expressed as mean ± standard deviation. Statistical comparisons were made using the Student t-test with Bonferroni’s correction. Statistical significance was accepted at the 95% confidence level (P < 0.05).

Results

Patient population

Table 1 summarizes the characteristics for patients with new-onset angina compared to those without angina at any time before their first Q-wave acute myocardial infarction. The two groups did not differ in terms of age, sex and classical risk factors for myocardial infarction. Similarly, there was no difference in body mass index, sedentary life style, and medical therapy. In particular, only a small number of patients were receiving drugs (for hypertension) that affect myocardial function. Aspirin was taken by six patients with new-onset angina and by four patients without angina at baseline. In contrast, in patients without angina there was a strong

Table 1   Characteristics of patients with new-onset angina who developed ischaemic episodes within 48 h compared to patients without prior angina at any time before their first acute Q-wave myocardial infarction

<table>
<thead>
<tr>
<th>Variables</th>
<th>New-onset angina (n=48)</th>
<th>No angina (n=42)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>52 ± 10</td>
<td>54 ± 9</td>
<td>ns</td>
</tr>
<tr>
<td>Male/female, n (%)</td>
<td>32 (66·6)</td>
<td>16 (33·3)</td>
<td>30 (71·4)</td>
</tr>
<tr>
<td>Body mass index (kg.m⁻², mean ± SD)</td>
<td>30 ± 1.5</td>
<td>29 ± 1.8</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>8 (16·6)</td>
<td>8 (19·0)</td>
<td>ns</td>
</tr>
<tr>
<td>Dyslipidaemias, n (%)</td>
<td>2 (4·1)</td>
<td>2 (4·7)</td>
<td>ns</td>
</tr>
<tr>
<td>Family history for coronary heart disease, n (%)</td>
<td>16 (33·3)</td>
<td>14 (33·3)</td>
<td>ns</td>
</tr>
<tr>
<td>Sedentary life style, n (%)</td>
<td>24 (50·0)</td>
<td>26 (61·8)</td>
<td>ns</td>
</tr>
<tr>
<td>Ever smoked, n (%)</td>
<td>40 (83·3)</td>
<td>36 (85·7)</td>
<td>ns</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>4 (8·3)</td>
<td>4 (9·5)</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium antagonists, n (%)</td>
<td>4 (8·3)</td>
<td>4 (9·5)</td>
<td>ns</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors, n (%)</td>
<td>2 (4·1)</td>
<td>2 (4·7)</td>
<td>ns</td>
</tr>
<tr>
<td>Nitrites, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>ns</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>6 (12·5%)</td>
<td>4 (9·5%)</td>
<td>ns</td>
</tr>
</tbody>
</table>
family history of coronary heart disease (P <0·05). However, the significance of this latter result should be viewed from the standpoint that from 14 comparisons one might expect one to show a significant statistical difference at random.

Electrocardiographic parameters

There was a trend towards a shorter reperfusion time in patients with new-onset angina compared to those in whom myocardial infarction occurred unheralded, although values were not significantly different (Table 2). Continuous ST-segment monitoring showed that pre-thrombolysis ST-elevation was similar between groups. \( \triangle ST \) elevation values were similar between groups both before and after thrombolysis (Table 2). SR waves were higher before and after thrombolysis in patients with prior angina; however, these values did not reach statistical significance (Table 2).

Time to reperfusion

As described in the methods section, the efficacy of thrombolysis was defined by the following criteria: continuous ST-segment monitoring, early MB-creatine kinase peak (<18 h), and sudden decrease in chest pain. When considering ECG parameters, there was a slight non-significant trend towards shorter reperfusion times in patients with new-onset angina (Table 2). In fact, the time to reperfusion was 41·3 ± 22·0 min in patients with new-onset angina compared to 52·5 ± 29·8 min in patients without angina (P =ns). Cardiac enzymes peaked at similar times between groups (10·8 ± 2·3 vs 11·9 ± 3·7 h, P =ns, 0·25). Finally, although patients with new-onset angina and short reperfusion times also had prompt regression of infarction symptoms, the sudden decrease in chest pain is a subjective parameter which cannot be measured accurately in relatively small groups of patients.

Infarct size determined by creatine kinase release

Patients with new-onset angina had smaller creatine kinase peak levels than patients without angina (976 ± 168 vs 1612 ± 328 IU . l \(^{-1} \), P <0·05). Similarly, the peak isoenzyme-MB creatine kinase level was significantly lower in patients with new-onset angina (96 ± 47 as compared with 221 ± 108 IU . l \(^{-1} \), P <0·01 compared to patients without preinfarction angina). The time course of MB-creatine kinase values is shown in Fig. 1. The area under the 36-h MB-creatine kinase curve was 1321 ± 876, as compared to 3879 ± 1555 IU . l \(^{-1} \) (P <0·01). These curves were also different statistically at each sampling point at the 8th and 20th hour.

Clinical outcome and 4-week follow-up

As shown in the upper panel of Table 3, the incidence of complications during the in-hospital outcome was similar between groups. Twelve patients with angina (25% of total patients) underwent angiography that showed the absence of collaterals (Table 3; lower panel). Similarly, the other variables considered during the 4-week follow-up were comparable between groups (Table 3; lower panel). We present these data only to support the concept that differences seen in echocardiographic parameters were not due to visible disparity in the incidence of complications during the in-hospital outcome and during the 4-week follow up. In fact, the number of patients involved is low with regard to clinical events and mortality. The statistical power to detect a clinical difference was 28%, with an odds ratio of 2·60 (for mortality rate), declining progressively to 14% and 6% with a declining odds ratio of 1·50 and 1·25 (which includes the incidence of arrhythmias and congestive heart failure, respectively).

Echocardiographic analysis

After acute myocardial infarction, global ventricular function was similarly depressed in both groups (Fig. 2). From the third day, ejection fraction became significantly greater in patients with pre-infarction new-onset angina. This difference persisted at the end of follow-up study (Fig. 2).

The wall motion score, indicating the degree of hypokinesis, improved sooner in patients with angina before acute myocardial infarction (Fig. 3(a)). These

<table>
<thead>
<tr>
<th>ECG parameters</th>
<th>New-onset angina (n=48)</th>
<th>No angina (n=42)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from onset of continuous chest pain to thrombolytic treatment (min, mean ± SD)</td>
<td>95±1 19±4</td>
<td>89±2 16±1</td>
<td>ns</td>
</tr>
<tr>
<td>Number of leads with ST elevation (mean ± SD)</td>
<td>3±± 0±9</td>
<td>3±± 0±8</td>
<td>ns</td>
</tr>
<tr>
<td>( \triangle ST ) at admission (mm, mean ± SD)</td>
<td>10±8 3±5</td>
<td>11±5 4±2</td>
<td>ns</td>
</tr>
<tr>
<td>( \triangle ST ) at the end of thrombolysis (mm, mean ± SD)</td>
<td>2±6 1±6</td>
<td>3±1 1±8</td>
<td>ns</td>
</tr>
<tr>
<td>SR waves on admission (mean ± SD)</td>
<td>44±5 16±6</td>
<td>33±9 13±2</td>
<td>ns (0·07)</td>
</tr>
<tr>
<td>SR waves at the end of thrombolysis (mean ± SD)</td>
<td>34±8 12±5</td>
<td>25±8 11±4</td>
<td>ns (0·14)</td>
</tr>
<tr>
<td>Time to reperfusion (min, mean ± SD)</td>
<td>41±3 22±0</td>
<td>52±5 29±8</td>
<td>ns (0·12)</td>
</tr>
</tbody>
</table>
latter results showed a more severe degree of hypokinesis in patients in whom myocardial infarction occurred unheralded. The degree of hypokinesis progressively decreased in both groups until the 3-month follow-up. Accordingly, the number of hypokinetic segments in the infarct-related area was smaller in patients with pre-infarction new-onset angina at each selected time-point (Fig. 3(b)). Differences were significant statistically from the 3rd day until 1 month-follow up.

In conclusion, in patients with pre-infarction new-onset angina, recovery of left ventricular function was earlier than in patients in whom myocardial infarction was unheralded.

**Discussion**

The major finding of our study is that recovery of myocardial contractile function after thrombolysis occurred earlier in patients in whom Q-wave myocardial infarction was preceded by new-onset angina, as compared to patients in whom infarction occurred unheralded.

Compared to patients with unheralded myocardial infarction, patients with angina prior to myocardial infarction had a better preserved left ventricular performance. The TAM I Study Group\(^{[17]}\) reported a less complicated short-term course and fewer episodes of...
reocclusion after thrombolysis in patients with angina one-week pre-infarction. Lacking significant reperfusion\textsuperscript{[15,16]}, preconditioning may not occur; however, lack of certain reperfusion in the context of chronically occluded coronary arteries does not exclude a preconditioning effect, particularly since preconditioning ‘at a distance’ is a well known phenomenon in experimental models\textsuperscript{[1,2]}. The difference in residual contractile function may have been due, in part to recruitment of collateral flow. Cortina et al.\textsuperscript{[18]} reported better preservation of ventricular function in patients with pre-infarction angina (ranged from 1 month to 8 years), but it was showed angiographically that collaterals play a significant protective role. More recently, Nakagawa et al.\textsuperscript{[8]} also showed the protective effect of previous angina in patients with reperfused anterior wall myocardial infarction. However, large studies have showed that those with angina do worse in terms of prognosis\textsuperscript{[19,20]}. Patients with antecedent stable angina are more likely to have multivessel coronary heart disease, and are prescribed several anti-ischaemic drugs that were taken for several months or years; these considerations can also affect the clinical outcome following myocardial infarction\textsuperscript{[3]}. In the present study, to minimize the impact of several variables, care was taken to select patients who developed new-onset angina within 48 h of their first Q-wave acute myocardial infarction. Although the time needed to develop new collaterals after acute coronary occlusion in humans is still unclear\textsuperscript{[21,22]}, Schwartz et al.\textsuperscript{[23]} showed that in man it takes about 2 weeks to develop new visible collateral vessels following myocardial infarction.

Previous studies\textsuperscript{[7,8,15–18]} evaluating ejection fraction included patients with a previous infarction or wall motion abnormalities. This may make it difficult to locate the occurrence of new wall motion abnormalities and thus recovery of contractile function over time.

A nother important issue is the use of antianginal drugs that may affect the contractile function. In the present study, only a very small number of patients were taking beta-blockers, calcium channel blockers, or angiotensin converting enzyme inhibitors, and we observed that new-onset angina was associated with improved myocardial recovery in patients not receiving these drugs.

Early administration of thrombolysis after acute myocardial infarction is crucial in both limiting

Figure 2. Bar graph showing left ventricular ejection fraction recovery at each selected time-point in patients with pre-infarction new-onset angina (\textsuperscript{[3]}) and in patients in whom infarction was unheralded (\textsuperscript{[2]}). *P<0.05 vs no angina patients. Data are mean ± standard error.

Figure 3. Bar graph showing the wall motion score at each selected time-point in patients with pre-infarction new-onset angina (\textsuperscript{[3]}) and in patients in whom infarction was unheralded (\textsuperscript{[2]}). *P<0.05 vs no angina patient. Data are mean ± standard error. (b) Bar graph showing the number of hypokinetic myocardial segments at each selected time-point in patients with pre-infarction new-onset angina and in patients in whom infarction was unheralded. *P<0.05 vs no angina patients. Data are mean ± standard error.
infarct size and preserving left ventricular function\textsuperscript{[24]}. Recently, Andreotti et al.\textsuperscript{[25]} proposed that in addition to ischaemic preconditioning benefit from pre-infarction angina, with respect to infarct size, may depend on faster coronary thrombolysis. We agree that new-onset angina may be associated with newly formed thrombi which are thrombolysed faster than isolated thrombi that have been allowed to grow\textsuperscript{[25]}. In the present study and that of Ottani et al.\textsuperscript{[26]} ECG continuous monitoring has revealed a trend towards shorter reperfusion times after thrombolysis in patients with angina before myocardial infarction than in those without angina. In addition, in our study the infarct was significantly smaller in patients with pre-infarction angina. Thus, the effects of new-onset pre-infarction angina seen in the present study may be, in part, related to the faster thrombolysis of patients with angina compared to those in whom acute myocardial infarction was un heralded.

It is possible that small changes in regional function may be undetected when routine techniques are employed. Episodes of myocardial ischaemia of a duration insufficient to induce necrosis may result in myocardial ‘stunning’\textsuperscript{[26]}. Stunning is quite common and could be identified in many clinical conditions, including patients with unstable angina\textsuperscript{[27]} variant angina\textsuperscript{[27]}, exercise-induced angina\textsuperscript{[28]}, and in patients with myocardial infarction reperfused by thrombolysis\textsuperscript{[27]}. This phenomenon might affect baseline wall motion in our patients. In this respect, in the present study the difference in the analysis of infarct zone regional function was compared to the respective baseline value. Therefore, each patient acted as his/her own control at each selected time-point. However, our patient population was selected according to several exclusion criteria, and thus our results may not be always applicable to all patients with new-onset angina pre-infarction angina.

It is not known how previous ischaemic episodes exert their protective role. Recently, it has been suggested that there is an ‘early’ powerful phase lasting only 1 h\textsuperscript{[3,2]} followed by a ‘late’ phase of preconditioning that disappears within 6 days\textsuperscript{[29,30]}. The studies carried out on the conscious pig model in which ‘late’ preconditioning was described\textsuperscript{[29,30]} showed that protection from post-ischaemic dysfunction disappears within 6 days. The induction of stress proteins is one of mediators of preconditioning\textsuperscript{[31]}, but cardioprotective proteins can be degraded within one week. Accordingly, in the present study the major effect on regional function was seen within one week of myocardial infarction, suggesting that it may be due, in part, to ‘late’ preconditioning. However, there has been no evidence of stress protein involvement in preconditioning against stunning in animal models, and late protection against infarct size does not exist in the pig model\textsuperscript{[32]}. Therefore, the pig model does not exclusively explain the results of the present study.

The efficacy of the late phase of preconditioning in reducing myocardial infarct size is still controversial. Kuzuya et al.\textsuperscript{[33]} demonstrated in open-chest dogs that a sequence of four 5-min coronary occlusions reduces the size of the myocardial infarction produced by a 90-min coronary occlusion applied 24 h later. Similarly, using open-chest rabbits, Marber et al.\textsuperscript{[34]} demonstrated that a sequence of four 5-min coronary occlusions significantly reduces the size of the myocardial infarction resulting from a 30-min coronary occlusion applied 24 h after the preconditioning ischaemia. Comparable results have been reported by Baxter et al.\textsuperscript{[35–37]} in a similar model. Delayed protection on infarct size was prolonged, extending between 24 and 72 h after the preconditioning stimulus; the threshold for eliciting the second window of protection was as low as one 5-min coronary occlusion\textsuperscript{[37]}. The time-course of adenosine A1-receptor activation-induced delayed myocardial protection (achieved with the selective agonist 2-chloro-N6-cyclopentyladenosine), and the elevation of the cytoprotective inducible 72-kDa heat-shock protein was also investigated\textsuperscript{[36]}. Transient adenosine A1-receptor activation induced a delayed and prolonged period of enhanced resistance to ischaemia in rabbit myocardium, but, as suggested by the authors, this was probably the result of an adaptive mechanism not involving elevation of heat shock proteins\textsuperscript{[36]}. Surprisingly, using an open-chest rabbit preparation and an experimental protocol similar to that of Marber et al.\textsuperscript{[34]} and Baxter and colleagues\textsuperscript{[35–37]}, Takanaka et al.\textsuperscript{[38]} failed to show a significant infarct-limiting effect either 24 or 48 h after the preconditioning ischaemia. To potentiate induction of heat shock proteins, a preconditioning protocol involving four 5-min episodes of ischaemia–reperfusion was also utilized and was separated from sustained ischaemia by 24 or 48 h of reperfusion\textsuperscript{[38]}. Neither of these protocols was protective, and limitation of myocardial infarct size was not observed\textsuperscript{[38]}. However, immunoreactivity (using a monoclonal antibody against 72- to 73-kDa heat shock protein) was seen in the myocardium at 24 and 48 h after preconditioning\textsuperscript{[38]}. In preliminary results, Jagasia et al.\textsuperscript{[39]} did not report any reduction in infarct size in open-chest rats subjected to a 45-min coronary occlusion 24 h after preconditioning with either three 3-min occlusions or one 15-min occlusion. The exact reason for these conflicting results is still unclear. In large animal species, the effects of ischaemic preconditioning have been variable\textsuperscript{[32–34]}, therefore the apparent discrepancy among the above studies may be explained by intrinsic differences in species, experimental preparations, and protocols. Obviously, the extrapolation of data from experimental models to complex pathophysiological mechanisms in man may be misleading. Ischaemic preconditioning also seems to exert a protective effect in isolated rat heart\textsuperscript{[40]}, in anaesthetised dogs and rats\textsuperscript{[41]}, and in-hospital life-threatening ventricular tachyarrhythmias and late potentials in patients with a first acute myocardial infarction\textsuperscript{[42]}. Although complete myocardial reperfusion is mandatory for preconditioning\textsuperscript{[43]}, it has been shown that the presence of a critical coronary artery stenosis does not abolish the protective effect of preconditioning\textsuperscript{[44]}. This phenomenon may be similar to the clinical scenario in which brief ischaemic episodes and

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reperfusion superimposed on a critical coronary stenosis precedes prolonged occlusion determining acute myocardial infarction. Thus, new-onset angina may be a representative clinical condition in which the presence of a critical stenosis does not abolish the beneficial effect of ischemic preconditioning.

In humans, silent ischemia may represent another source of the total ischemic burden. This evidence was applied to both groups of patients. However, it has been shown that patients with symptomatic ischemic episodes has a higher rate of silent ischemic episodes than asymptomatic patients.[45] On the other hand, patients with unstable angina had relatively few episodes of silent ischemia (15%)[46]. To date, we really do not know when and to what extent patients with new-onset angina had transient myocardial ischemia.

We only included patients younger than 65 years because recent evidence by A bete et al.[47,48] shows that there is an age-related loss of ischemic preconditioning in the ageing heart. This latter mechanism may contribute to the higher mortality observed in ageing patients with myocardial infarction.[49,50]

In conclusion, our data show that in patients with new-onset angina there is a better recovery of regional function after thrombolysed infarction. Our finding is consistent with the hypothesis that brief ischemic episodes immediately before acute myocardial infarction may precondition the human heart.

References


