Angina pectoris in patients with a history of myocardial infarction

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The existence of a history of myocardial infarction (MI) in patients with angina pectoris is frequently associated with certain patient characteristics, including an established history of coronary artery disease (CAD), depressed left ventricular function in some patients and multivessel coronary disease.

Angina is a symptom which reveals the persistence or recurrence of myocardial ischaemia. It is uncertain whether persistent myocardial ischaemia after MI is an adverse prognostic factor. In fact, the most important known prognostic factor is left ventricular function.

Before choosing an anti-anginal therapy in patients with a history of MI, coronary angiography should be performed in order to investigate the possibility of left main or multivessel CAD. Angina patients with impaired left ventricular function may benefit from revascularization but the prognostic value of percutaneous transluminal coronary angioplasty in these patients remains to be assessed. Medical anti-anginal therapy for symptoms, added to routine background treatment, is indicated when the results of revascularization are unsatisfactory or if there is an absence of indication, or a contra-indication, for revascularization procedures. Particular attention should be paid to the possible additive negative inotropic or chronotropic effects of β-blockers and certain calcium antagonists on the myocardium (Eur Heart J 1996; 17 (Suppl G): 25-29)

Key Words: Angina pectoris, myocardial infarction, calcium channel blockers

Introduction

Angina pectoris and myocardial infarction (MI) are among the most frequently observed aspects of coronary artery disease (CAD) and in some patients these two complications may occur successively. It has been reported that half of the patients with MI will have angina pectoris during follow-up[1-7], while databases from some studies show that, on average, half of the patients with angina pectoris have a history of MI (Table 1).

Among these patients, some have had an MI very recently and this early post-infarction angina is an acute form of CAD that poses specific problems in terms of investigation and therapeutic approach[11]. However, in this review, the objective is to focus only on patients with angina pectoris and history of a previous MI (at least 1 month before).

Three questions remain to be answered: (1) what are the main characteristics of these patients with angina pectoris and a history of MI; (2) what is the prognosis related to these characteristics; (3) what is the best therapeutic approach with regard to investigation, revascularization procedures and medical therapy?

Table 1 Frequency of a history of myocardial infarction in patients with anginal pectoris

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>No. of patients with a history of MI</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASS[8]</td>
<td>780</td>
<td>467</td>
<td>59</td>
</tr>
<tr>
<td>ECSSG[9]</td>
<td>768</td>
<td>349</td>
<td>45</td>
</tr>
<tr>
<td>VA study[10]</td>
<td>686</td>
<td>411</td>
<td>60</td>
</tr>
</tbody>
</table>

CASS=Coronary Artery Surgery Study; ECSSG=European Coronary Surgery Study Group; MI=myocardial infarction; VA=Veterans Administration.

Characteristics of patients

Patients with angina pectoris and a history of MI have some special characteristics. For example, the risk of recurrence of angina pectoris after MI is increased by 50% (79% vs 52%, P<0.01)[3] in patients who have a previous history of angina. It has also been shown that recurrent angina after MI is more common in patients with non-Q wave infarction[12], in whom the risk is increased by 40% (65% vs 46%, P<0.0001).

Furthermore, it has been shown that angina pectoris is more frequently observed in the follow-up after MI in patients with two- (68%) or three-vessel
disease (77%) than in patients with one-vessel disease (36%, \( P<0.025 \)). This risk is also increased in patients with proximal left anterior descending (LAD) lesions\[^3\].

On average, patients post-MI usually exhibit some degree of depressed left ventricular function, proportionally related to the extent of necrosis, but such differences do not appear to be linked to the presence or absence of angina pectoris\[^3\]. Furthermore, it has been shown that left ventricular function in patients with one healed MI did not differ between patients with or without exercise-induced angina pectoris and ST depression during exercise testing\[^13\].

In summary, the existence of a history of MI in patients with angina pectoris is frequently associated with certain patient characteristics, including an established history of CAD, depressed left ventricular function in some patients and multi-vessel disease.

**Prognosis**

Angina pectoris is a symptom revealing the persistence or the recurrence of myocardial ischaemia after MI. However, many studies have demonstrated that myocardial ischaemia is mostly asymptomatic and is four-times more frequent than symptomatic disease\[^16\]. Therefore, assessment of the prognosis of patients with angina pectoris and a history of MI is more accurately addressed by evaluating the importance of myocardial ischaemia itself. This can be done by any non-invasive investigation routinely used for detection of myocardial ischaemia, of which exercise testing is the most frequently performed. In 1979, Theroux et al.\[^15\] reported that the presence of ST depression during an early exercise test after MI was predictive of subsequent cardiac events. Since then, many studies have been performed to assess the predictive value of exercise-induced ischaemia soon after MI, often with negative results\[^16\]. The presence of ischaemic episodes on 24-h ambulatory ECG monitoring has been shown to predict cardiac events\[^17\], but those events which are predicted are often 'soft' events, such as coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG), and not 'hard' events, such as death or recurrent MI. More recent studies, using left ventricular contraction abnormalities detected by echocardiography as a marker of ischaemia, have shown interesting results as regards prognosis evaluation\[^18\]. In one study, the clinical outcome was predicted with a good sensitivity (80%) and a high specificity (95%). However, in general, the presence of angina pectoris and, above all, myocardial ischaemia after MI, is a controversial prognostic factor, with probably little predictive value of death and recurrent MI.

If the prognostic value of myocardial ischaemia is unclear, left ventricular function is definitely an important prognostic indicator. Cardiac mortality in the first year after MI is directly related to left ventricular ejection fraction (Fig. 1), with a rapidly increasing risk in the case of ejection fraction <0.40\[^19\]. As has been indicated above, patients with angina pectoris and a history of MI generally have some degree of depressed left ventricular function. Long-term prognosis is therefore directly related to left ventricular ejection fraction, with a high risk of subsequent cardiac events in the case of severely depressed left ventricular function.

**Treatment of angina pectoris after myocardial infarction**

*Medical treatment*

Routine background medical treatment post-MI is now well established and many classes of drugs have a beneficial effect on the long-term prognosis and symptoms of these patients\[^20\]. \( \beta \)-blockers, anti-platelet agents, anti-coagulants and cholesterol-lowering agents have proven efficacy in secondary prevention (Table 2). To these drugs, cardiac rehabilitation must be added as being a beneficial treatment in post-MI patients\[^20\].

On the other hand, class-I anti-arrhythmics have a detrimental effect\[^21\]. More recently, the efficacy of angiotensin converting enzyme inhibitors has been demonstrated, especially for prevention of left ventricular re-modelling and long-term improvement of prognosis in patients with depressed left ventricular function\[^22\].

Among the different drugs which may be prescribed in post-MI patients, particularly in cases of recurrent angina pectoris, the position of calcium channel blockers is questionable. Although their anti-anginal efficacy is proven, no overall beneficial influence on long-term prognosis has been demonstrated\[^20\]. But this effect differs according to the type of agent which is used\[^23\]. The analysis of the different published trials (Table 3) shows a trend in favour of agents that decrease heart rate (diltiazem and verapamil) in terms of long-term mortality (risk ratio: 0.95, 95% confidence interval: 0.82–1.09, ns) and reinfarction rate (risk ratio: 0.79, 95% confidence interval: 0.67–0.94, \( P<0.01 \)). However, agents such as some dihydropyridines that increase heart rate have been shown to be associated with a non-significant trend towards a detrimental effect on
Table 2 Cumulative meta-analyses of treatments of myocardial infarction and secondary prevention. (Reproduced with permission from Lau et al.[20])

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of trials</th>
<th>No. of patients</th>
<th>Cumulative odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-coagulants</td>
<td>12</td>
<td>4975</td>
<td>0.78 (0.67-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>23</td>
<td>5022</td>
<td>0.80 (0.67-0.95)</td>
<td>0.012</td>
</tr>
<tr>
<td>β-blockers</td>
<td>17</td>
<td>20 138</td>
<td>0.81 (0.73-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol lowering</td>
<td>8</td>
<td>10 775</td>
<td>0.86 (0.79-0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-platelet agents</td>
<td>10</td>
<td>18 411</td>
<td>0.90 (0.82-1.00)</td>
<td>0.051</td>
</tr>
<tr>
<td>Ca²⁺ channel blockers</td>
<td>6</td>
<td>13 114</td>
<td>1.01 (0.90-1.12)</td>
<td>0.91</td>
</tr>
<tr>
<td>Class I anti-arrhythmics</td>
<td>11</td>
<td>4336</td>
<td>1.28 (1.02-1.61)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 3 Effects of calcium antagonists on long-term prognosis after myocardial infarction. (Reproduced with permission from Yusuf et al.[23])

<table>
<thead>
<tr>
<th>Mortality</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>(95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines</td>
<td>714</td>
<td>1.16</td>
<td>0.99-1.35</td>
<td>ns</td>
</tr>
<tr>
<td>Verapamil+diltiazem</td>
<td>871</td>
<td>0.95</td>
<td>0.82-1.09</td>
<td>ns</td>
</tr>
<tr>
<td>Reinfarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>257</td>
<td>1.19</td>
<td>0.92-1.53</td>
<td>ns</td>
</tr>
<tr>
<td>Verapamil+diltiazem</td>
<td>564</td>
<td>0.79</td>
<td>0.67-0.94</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

mortality (risk ratio: 1.16, 95% confidence interval: 0.99-1.35, ns) and reinfarction rate (risk ratio: 1.19, 95% confidence interval: 0.92-1.53, ns).

Within calcium channel blockers, agents which decrease heart rate have no effect[24] or even a slightly detrimental effect[25] on long-term prognosis in patients with congestive heart failure.

The presence of angina pectoris in patients with a history of MI suggests that the routine background treatment is insufficient. In these conditions many anti-anginal drugs may be of benefit in controlling symptoms, as well as myocardial ischaemia. Among these, nitrates, especially long-acting nitrates, or calcium antagonists may be prescribed, usually on top of optimal β-blocker background treatment. Long-acting nitrates are an interesting alternative which are widely used, especially with β-blockers, for the treatment of angina pectoris. However, reductions in efficacy have been demonstrated in long-term therapy, due to the appearance of nitrate tolerance[26]. Therefore, the control of symptoms in these patients is often based on additional treatment with calcium antagonists. Of these agents, amlodipine[27] (Fig. 2) and verapamil[27] (Fig. 3) have proven symptomatic efficacy in this population of patients. It has also been demonstrated that calcium antagonists are efficient in reducing the frequency of silent ischaemic episodes. Furthermore, they have complementary effects when associated with β-blockers, since the latter are effective for the treatment of ischaemic episodes associated with an increase in heart rate, while calcium antagonists are more effective for ischaemic episodes not related to such an increase[28]. They may be used in addition to β-blockers or as monotherapy, when β-blockers are contra-indicated. In the latter case, the choice of the calcium antagonist must be based on its impact on long-term prognosis. Although diltiazem has been shown to result in a reduction in cardiac events for a period of between 12 and 52 months post-MI, this was counter-balanced by an increase in such events in those patients with left ventricular dysfunction[25]. Therefore, the only drug of this class to have proven efficacy at this time is verapamil.

In the case of an addition to β-blockers, no data are available on the potential effects of combination

![Figure 2](Figure 2: The total number of anginal attacks/h during 2-week baseline and final 2 weeks of amlodipine treatment. Based on diary data from evaluable post-myocardial infarction patients (baseline n=47). * = baseline; O = final (Reproduced with permission from Taylor[27].)
therapy on prognosis. However, it may be supposed that 
\( \beta \)-blockers and calcium antagonists with negative 
chronotropic action, and perhaps those with no effect on 
heart rate, have a beneficial additive effect on prognosis. 
However, key limiting factors in long-term therapy are 
the additive effects of both classes of drugs on contrac-
tility, heart rate (for those with a negative chronotropic 
effect), blood pressure and atriioventricular conduction, 
which should lead to some caution in initiating and 
continuing such combination treatment because of the 
high frequency of impaired left ventricular function in 
post-MI patients.

Calcium antagonists have another interesting 
effect in patients with angina pectoris who are likely to 
have a depressed myocardial function, in that it has been 
shown that they may improve diastolic function, which 
is often altered in patients with CAD.

Thus, the medical treatment of angina pectoris in 
patients with a history of MI may include nitrates or 
calcium antagonists on top of the background treatment 
(usually including \( \beta \)-blockers) that is routinely pre-
scribed post-MI. In terms of being effective both on 
symptoms and prognosis, the best choice is a calcium 
antagonist with a negative chronotropic effect (or, at 
least, no positive chronotropic effect), although one 
must be cautious about the additive effects of both 
classes of drugs on the myocardium. In case of contra-
indication to \( \beta \)-blockers, verapamil has proven sympto-
matic and prognostic efficacy when left ventricular 
systolic function is not depressed. However, while cal-
cium antagonists have a beneficial effect on symptoms, 
there is no evidence at the present time that any drugs of 
this class have a beneficial effect on prognosis.

Revascularization procedures

No specific data concerning the prognostic influence of 
myocardial revascularization for angina pectoris after 
MI in large populations are available. However, large 
trials comparing medical and surgical treatment in 
patients with angina pectoris include a significant pro-
portion of patients with a history of MI and this enables 
us to draw some conclusions. From these data it has 
been proven that patients who may benefit from aorto-
coronary bypass surgery include those with an ejection 
fraction <0.5[8], patients with two- or three-vessel dis-
ease, including proximal LAD lesions[9] and patients 
with left main coronary artery lesions[10].

Even if these results do not exclusively concern 
patients with a history of MI, they may be the basis of a 
routine approach towards angiography in patients 
with a history of MI. The first step in such a therapeutic 
approach is to perform coronary angiography and then 
to refer patients to surgery if coronary artery lesions and 
left ventricular function indicate that this is appropriate.

PTCA represents an alternative means of myocar-
dial revascularization but it is contra-indicated in 
some cases, such as left main stenosis. It is also less likely 
to obtain complete revascularization than surgery in 
multivessel disease and its usefulness is limited by the 
restenosis rate. PTCA also suffers from the lack of data, 
based on large populations, regarding the possible bene-
ficial effect of revascularization on long-term prognosis 
in post-MI patients[30]. Even if the concept of an 'open 
artery' is interesting, no data are available regarding the 
value of re-opening the infarct-related artery in post-MI 
patients. The only clear indication for PTCA is the 
persistence of symptoms of angina pectoris, in spite of 
optimal anti-anginal therapy associated with one- or 
two-vessel disease and nearly normal left ventricular 
function.

In summary, the presence of angina pectoris in 
patients with a history of MI is an indication first to 
perform coronary artery angiography, due to the high 
incidence of two- or three-vessel disease and depressed 
left ventricular function in this population. The decision 
as to whether to undertake revascularization and the 
choice of method used should be based on the extent 
of coronary artery lesions and left ventricular function, 
together with findings from clinical and non-invasive 
investigations.

Medical anti-anginal therapy for symptoms, 
added to routine background treatment, is indicated 
when the results of revascularization are unsatisfactory 
or if there is an absence of indication or a contra-
indication for revascularization procedures.

Conclusions

Patients with angina pectoris and a history of MI are 
likely to have a history of previous angina pectoris or a 
history of non-Q-wave MI and often have two- or three-
vessel disease and depressed left ventricular function.

Despite the fact that the presence of symptoms 
or the persistence of myocardial ischaemia after MI has 
a questionable effect on long-term prognosis, there is an 
accumulation of data suggesting that they have little 
impact on subsequent cardiac 'hard' events.

The best therapeutic approach to these patients, 
based on the main characteristics of this population, is
to perform coronary artery angiography followed by revascularization by CABG or PTCA, if necessary, according to the extent of lesions and symptoms and to add long-acting nitrates or calcium antagonists to the usual background β-blocker treatment, paying particular attention to the possible additive negative inotropic or chronotropic effects of β-blockers and calcium antagonists on the myocardium. If β-blockers are contra-indicated, calcium antagonists which have a proven beneficial effect on symptoms and long-term prognosis should be used.

References


