Treatment effects on the total ischaemic burden and prognostic implications

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Anginal symptoms alone are not a reliable guide to the extent of patients’ ischaemic heart disease and silent episodes of ischaemia are associated with increased morbidity and mortality. It is becoming apparent that effective treatment of ischaemia will have to target the pattern of ischaemic events seen in patients’ daily lives and treatment strategies are now being developed which aim to eliminate both silent and symptomatic episodes of ischaemia over the whole 24-h period. For example, the Circadian Anti-ischemia Program in Europe (CAPE) trial has shown that significant improvements in objective and subjective measures of ischaemia occurred over 24 h when the once-daily, third-generation dihydropyridine calcium antagonist amlodipine was added to background medical therapy. In addition, the Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) has clearly shown the complementary effects of combination therapy with amlodipine and the long-acting β-blocker atenolol. Ongoing and future outcome studies will determine the impact of such approaches on the prognosis for patients with ischaemic heart disease. (Eur Heart J 1996; 17 (Suppl G): 64-68)

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Introduction

Physicians who treat patients with coronary artery disease (CAD) and transient myocardial ischaemia aim not only to relieve symptoms, but also to reduce morbidity and mortality. Angina pectoris may result from an increase in myocardial oxygen demand and/or a reduction in coronary blood supply and it responds to therapy with nitrates, β-blockers and calcium channel blockers used either alone or in combination. However, it is now recognized that anginal symptoms provide an underestimate of the true burden to transient myocardial ischaemia because silent (asymptomatic) episodes, which can be objectively assessed during normal daily activities by recording ST-segment deviation using continuous ambulatory ECG (Holter) monitoring, outnumber those accompanied by angina pectoris by three times or more[11-3].

The prognostic significance of myocardial ischaemia

The question of whether such objective evidence of ischaemia is merely a reflection of adverse events going on in the atherosclerotic plaque, or whether it is actually causally related to some of the cardiovascular events we would like to prevent, is a crucial issue which will direct attempts at risk reduction in different ways. If ischaemic activity reflects adverse events in atherosclerotic lesions, then it is reasonable to monitor for transient myocardial ischaemia as a guide to risk but not necessarily beneficial to suppress ischaemia over and above relief of symptoms in order to reduce coronary events. However, if ischaemia is a direct cause of these events, then all ischaemic activity (silent and symptomatic) should be considered not just in terms of risk stratification, but also as an endpoint of treatment in itself.

Several studies have now demonstrated increased morbidity and mortality associated with transient myocardial ischaemia during normal daily life[4-6] across the whole spectrum of patients with CAD, including those with unstable angina[7], chronic stable angina[8], peripheral vascular disease[9] and after myocardial infarction (MI)[9,10]. These findings suggest that exploring the pattern of triggers of transient myocardial ischaemia in daily life may be useful in order to improve our understanding of the underlying pathophysiology and to develop the optimal approach to treatment.

The pathophysiology and circadian rhythm of myocardial ischaemia

A characteristic circadian distribution of both painful and painless myocardial ischaemia can be observed, with a peak of ischaemic activity in the early morning hours.
and a trough during the night when patients with chronic stable angina are monitored during normal daily life\textsuperscript{111}. The occurrence of major events such as MI\textsuperscript{111} and sudden death\textsuperscript{111} mirror this pattern of ischaemia and this different picture of 'continuous risk' throughout the whole 24-h period contrasts with the traditional view of an episodic process characterized by brief periods of ischaemia accompanied by pain.

Most episodes of ischaemia are associated with increases in heart rate (myocardial oxygen demand) and follow the typical circadian rhythm (Fig. 1), with a morning peak period of occurrence and a lower peak in the afternoon, whereas a minority occur throughout the day and night, without increases in heart rate, which suggests that episodic vasospasm may be involved\textsuperscript{111}. In the study reported by Andrews \textit{et al.}\textsuperscript{141}, type 1 episodes occurred during a period of increased heart rate, type 2 episodes occurred within 10 min after a period of increased heart rate and type 3 episodes occurred without an increase in heart rate. It was found that the $\beta$-blocker propranolol had its greatest effect on the ischaemic episodes associated with high heart rates rather than on those occurring at lower heart rates. In contrast, the dihydropyridine calcium antagonist nifedipine was more effective against the episodes occurring at low heart rates (Fig. 2).

Evidence has come from observations of episodes of transient myocardial ischaemia by ambulatory ST-segment monitoring and more direct examination of myocardial perfusion, using techniques such as positron emission tomography, that the complex pathophysiology of ischaemia involves fluctuations in flow in atherosclerotic arteries in response to physiological stresses. Ordinary daily activities such as mental stress\textsuperscript{151}, cold exposure\textsuperscript{161}, exercise\textsuperscript{161} and cigarette smoking\textsuperscript{171} may result in ischaemia with both an increase in myocardial oxygen demand and a major decrease in coronary blood flow to the ischaemic myocardium, which contributes to the genesis of both symptomatic and asymptomatic myocardial ischaemia. Disturbed control of coronary blood flow may be mediated by dysfunction of the vascular endothelium with loss of key regulatory mechanisms such as the production of nitric oxide (endothelium-derived relaxing factor). Improvement of endothelial-dependent vascular responses is, therefore, a potentially novel therapeutic approach to anti-ischaemic therapy. Established clinical agents such as calcium channel blockers and angiotensin converting enzyme inhibitors may also have beneficial effects on endothelial function and the vascular walls in addition to direct effects on coronary and peripheral vascular smooth muscle\textsuperscript{18,19}.

**Reduction of the total ischaemic burden**

Effective treatment of ischaemia will have to target the pattern of ischaemic events seen in patients' daily lives. Revascularization strategies and drugs which effectively relieve angina also reduce silent myocardial ischaemia. However, because silent episodes usually outnumber those associated with angina pectoris, they may persist in patients who have been rendered free of symptoms by treatment. It has been suggested that between one-third and half of patients with chronic stable angina pectoris, treated with conventional agents, had ongoing myocardial ischaemic episodes during continuous monitoring\textsuperscript{20,21}. As it is known that different classes of agents have differential effects on the various types of ischaemic episodes, efforts have concentrated on the development of treatment strategies which target both symptomatic and asymptomatic myocardial ischaemia over the whole 24-h period in daily life. Long-acting agents which are effective throughout the whole 24-h period have obvious advantages. $\beta$-blockers such as metoprolol, bisoprolol and atenolol\textsuperscript{111,22–24} are effective but first-generation, short-acting calcium channel blockers such as nifedipine.
have proved disappointing because of their unsatisfactory pharmacokinetics and uneven plasma levels over the 24 h. This may result in undesirable vasodilator side effects, reflex sympathetic activation and an unpredictable dose–response relationship in individual patients. In contrast, when used with a novel extended release delivery system, the Gastro-Intestinal Therapeutic System (GITS), nifedipine has been shown to reduce ischaemia significantly in a large, multicentre trial in 207 patients with chronic stable angina, both as monotherapy and when combined with a β-blocker. The latter regimen was particularly effective against the morning surge in ischaemia, which was almost abolished.

Amlodipine, a newer third-generation calcium channel blocker (Fig. 3), represents a further development. Its intrinsically long half-life without the need for a ‘delivery system’ is potentially advantageous, particularly when drugs are taken irregularly, as is often the case in clinical practice. Amlodipine significantly reduced the total ischaemic burden over 24 h in comparison with placebo (Figs 4 and 5) in a large, multicentre trial, the Circadian Anti-ischaemia Program in Europe (CAPE), in which patients with chronic stable angina were randomized to treatment with either amlodipine 5 or 10 mg once daily (n=202) or placebo (n=113), in addition to background medical therapy, which included β-blockers in 63% of amlodipine-treated and 67% of placebo-treated patients and aspirin in 56% of both groups. However, the underlying circadian variation of ischaemia was not completely abolished as peaks in the morning and afternoon were still present though substantially attenuated (Fig. 5). Objective improvements in ischaemia on Holter monitoring with amlodipine were also accompanied by significant reductions in angina attacks and nitroglycerin consumption in comparison with placebo. Furthermore, amlodipine and placebo had similar safety profiles and there was no increase in heart rate associated with amlodipine treatment.

In view of the findings which suggest that ischaemic episodes are associated with either elevated heart rates or episodic vasoconstriction, it is rational to consider combination therapy with agents that act against both of these pathophysiological mechanisms. In the Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS), which involved 100 patients with stable CAD, the combination of amlodipine and atenolol was significantly more effective than either agent alone, as demonstrated by continuous monitoring and exercise testing, and confirmed the potential advantage of a combination of these two long-acting drugs. Amlodipine and the combination prolonged exercise time to 0·1 mV ST depression by 29% and 34%, respectively (P<0·001), vs 3% for atenolol (ns). In contrast, during continuous monitoring, the frequency of ischaemic episodes decreased by 28% with amlodipine (P=0·083), by 57% with atenolol (P<0·001) and by 72% with the combination (P<0·05 vs both single drugs and P<0·001 vs placebo). Suppression of ischaemia during exercise testing and ambulatory monitoring was similar in patients with and without exercise-induced angina. The exercise time to angina improved by 29% with amlodipine (P<0·01), by 16% with atenolol (P=0·05) and by 39% with the combination (P<0·005 vs placebo and both single drugs). In patients with angina, the total exercise time was increased by 16% with amlodipine (P<0·001), by 4% with atenolol (ns) and by 19% with the combination.
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Figure 5 Circadian pattern of transient ischaemic episodes during baseline and final monitoring in amlodipine- and placebo-treated patients. Amlodipine reduced ischaemia over the 24 h but the circadian pattern was unchanged. (Adapted with permission from Deanfield et al.128.)

(P<0.05 vs placebo and both single drugs). In those without angina, no drug therapy significantly improved total exercise time. Thus, the CASIS study has clearly shown the complementary effects of amlodipine and atenolol and the value of their use in combination. Ischaemia during treadmill testing was more effectively reduced by amlodipine, whereas ischaemia during continuous monitoring was more effectively reduced by atenolol. Combination therapy was more effective than either single drug against both types of ischaemia. A further amlodipine trial (CAPE II) is in progress to investigate the efficacy of amlodipine monotherapy and to determine the optimal combination of agents for reduction of transient myocardial ischaemia.

Conclusion

The recent debate about the role of calcium channel blockers in the treatment of myocardial ischaemia has emphasized the need for a rigorous prospective clinical evaluation of the effects of all anti-ischaemic agents on morbidity and mortality. Small-scale studies have suggested that suppression of ischaemia by medical treatment may be beneficial but these trials have not been of sufficient power to examine hard clinical endpoints. This key question is being addressed by a large NIH-sponsored prospective trial, the Asymptomatic Cardiac Ischemia Program (ACIP)30, which in its 1-year pilot phase compares medical treatment of angina with medical treatment of ischaemia and revascularization by angioplasty or surgery. Six-hundred patients with documented CAD and active ischaemia on exercise testing and ambulatory ST-segment monitoring (with and without symptoms) were successfully randomized to these three treatment approaches. The proposed long-term major trial will address morbidity and mortality associated with these therapeutic approaches. In the future our improved understanding of the functional components of CAD should allow the development of therapeutic strategies which will not merely produce benefits in terms of improvements in symptoms, but also result in reduction of major complications and prolongation of survival.

References


