Mechanisms whereby calcium channel antagonists may protect patients with coronary artery disease

L. H. Opie

Ischaemic Heart Disease Research Unit of the Medical Research Council, University of Cape Town Medical School, Cape Town, South Africa

Calcium antagonists have multiple mechanisms whereby they are able to protect against myocardial ischaemia. Recently questions have been posed about the long-term safety of this group of agents. This article is a selective rather than a complete review of the problems. Fears have largely centred around rapidly acting nifedipine when inappropriately used. This agent remains useful in Prinzmetal’s angina, a condition in which there are no long-term comparative outcome studies. Current evidence is that verapamil is as safe and as effective as the beta-blocker in effort angina and that non-dihydropyridines (verapamil and diltiazem) are efficacious in the follow up of non-Q wave infarct. Verapamil post-infarct is safe and reduces reinfarction, provided that clinical heart failure is first excluded.

(Eur Heart J 1997; 18 (Suppl A): A92–A104)

Key Words: Calcium antagonists, angina, myocardial protection, safety, efficacy, post-infarct.

Introduction

Calcium channel antagonists are certainly able to provide symptomatic relief in patients with angina pectoris and to reduce an elevated blood pressure in those with hypertension. Currently, however, probing questions are being put about the long-term benefits of all types of cardiovascular agents including calcium antagonists. Are they likely to protect or harm patients with coronary artery disease? What is their real long-term safety? This article reflects the personal views of the author on the use and long-term safety of calcium channel antagonists in ischaemic syndromes ranging from angina of effort to post-myocardial infarct follow-up and heart failure. Safety in hypertension has been discussed elsewhere and is not considered here, beyond stating that it is the belief of the present author that case-controlled studies have inherent defects that do not provide more than circumstantial evidence, and that the result of current prospective randomized outcome studies should be awaited.

Mechanism of antianginal and related protective effects of calcium channel antagonists

The mechanism of the clinical anti-ischaemic effects is complex, multifactorial and probably at least to some extent different between the dihydropyridines and other types of calcium channel antagonists.

Coronary vasodilation and increased oxygen supply

Because the calcium channel antagonists as a group are major vasodilators, they should improve myocardial oxygen delivery. Experimentally, coronary vasoconstriction induced by norepinephrine during exercise is improved by calcium channel antagonists, which increase the blood flow particularly in the subendocardial zones. Such vasoconstriction represents increased coronary vascular tone and should be distinguished from focal spasm. In addition, the lumen area at the site of coronary stenosis decreases during exercise in patients with coronary artery disease, regional myocardial blood flow falls during rapid atrial pacing. Calcium channel antagonists restore the flow towards normal. Thus, there is reasonable evidence that calcium channel antagonists could act by increasing coronary blood flow, especially of coronary resistance vessels. Logically, they should be more effective when there is a collateral flow to the ischaemic zone, and in patients with clinical evidence of coronary vasoconstriction, as for example in cold-induced angina. Calcium channel antagonists also relieve the additional decrease in stenosis size caused by exercise, as do the nitrates. Such anti-stenotic effects of the calcium channel antagonists may be additive to those of nitrates.
Decreased myocardial oxygen demand

Three of the major determinants of myocardial oxygen uptake are heart rate, blood pressure, and the contractile state of the myocardium. Calcium channel antagonists can influence each of these but variably. First, peripheral vasodilatation reduces blood pressure. This effect appears to be common to all calcium channel antagonists except for the mixed sodium–calcium antagonist, bepridil, which is nonetheless an anti-anginal agent. Second, some agents, especially diltiazem and verapamil, tend to reduce heart rate. In contrast, short-acting nifedipine tends reflexly to increase heart rate which is generally an unwanted effect in the therapy of angina. Third, verapamil and diltiazem exert a direct negative inotropic effect, thereby reducing oxygen demand and having a beta-blocker-like beneficial action.

The effects of acute and chronic therapy by calcium channel antagonists may differ, particularly with the dihydropyridines in which the initial tachycardia appears to become less with time. In addition, truly long-acting dihydropyridines will not cause acute repetitive vasodilation and should therefore avoid repetitive reactive tachycardia. Due to these differing effects on the balance between myocardial oxygen demand and supply, it is not possible to generalize concerning the antianginal mechanisms of the major types of calcium channel antagonists. Nonetheless, it is clear that verapamil and diltiazem act to reduce myocardial oxygen demand (heart rate and blood pressure decrease, contractility, although comparatively less), whereas the dihydropyridines have more variable effects.

Decreased reperfusion injury in animal models

Although it has long been proposed that myocardial calcium overload can cause reperfusion damage after myocardial ischaemia, only recently has it been shown that some of this damage can specifically be inhibited by calcium channel antagonists added only at the time of reperfusion[7]. Some of this protection may be mediated by the newly discovered antioxidant properties of calcium channel antagonists[8]. As will be discussed later, these properties must still be shown to be clinically relevant. In addition, when added before or during early ischaemia, calcium channel antagonists may also inhibit reperfusion injury by an anti-ischaemic mechanism[9]. In a few experiments, calcium channel antagonists added after the onset of reperfusion[10] have also lessened ischaemic injury, although these findings are challenged[11].

While modification of reperfusion injury cannot be expected to alter the time of onset or the severity of angina pectoris, nonetheless it may alter the rate of recovery from an anginal attack, an aspect seldom measured in clinical trials.

Direct cellular anti-ischaemic effect

Apart from influencing the myocardial oxygen supply–demand relationship, the calcium channel antagonists can also have a variety of direct anti-ischaemic cellular effects[12,13]. A real problem is that several of these 'direct effects' have been obtained with supratherapeutic doses of the various calcium channel antagonists. For example, the altered rate of ATP synthesis by mitochondria, resulting from inhibition of sodium-induced calcium release, was achieved by a diltiazem concentration of 4.5 x 10^{-9} M[14]. In contrast, the therapeutic molar value of free diltiazem is calculated at about 1-5 x 10^{-8} M[15] or about 100 x lower. In the case of other calcium channel antagonists, the concentrations required to inhibit sodium-induced calcium release from mitochondria are even higher. In a comparative study of isolated rat hearts, the concentrations of calcium channel antagonists required to inhibit ischaemia-induced enzyme release were all about 10^{-7} M, values which exceeded therapeutic levels in man by about 10-fold[16]. Therefore, the present author is not convinced of the clinical relevance of the experimentally found direct anti-ischaemic effect of calcium channel antagonists.

Vascular protective effects

Experimentally, calcium channel antagonists have an impressive number of other protective effects acting through a variety of mechanisms not necessarily involving tissue calcium channels.

Endothelial protection

Endothelial protection may be achieved by a variety of mechanisms including inhibition of synthesis of endothelin[17], inhibition of the vasoconstrictive effects of endothelin, enhancement of endothelium-dependent relaxation[18], by an antioxidant effect (next section) and by decreased intravascular pressure. All these should lead to improved endothelial integrity. Of specific interest is that one of these studies[17] was conducted with a concentration of nisoldipine (10^{-5} M) found in circulating blood in humans given the drug. However, should be considered that the binding of nisoldipine to plasma proteins is over 99%, so that the free concentration is close to 10^{-10} M. Hence it is of greater interest that calcium antagonists (nicardipine and diltiazem) prevent the abnormal vasoconstrictive response of stenotic coronary arteries to dynamic exercise in hypertensive patients, and that this change probably reflects improved endothelial integrity[19].

Antioxidant effect

An antioxidant effect may explain some of the anti-atheroma properties[8,19]. Earlier reports suggested variable antioxidant properties of the different agents and from experiment to experiment. For example, very high concentrations of nifedipine (10^{-3} M) are reported to be
either the most effective antioxidants of the calcium channel antagonists[22] or not effective at all[23]. Micromolar concentrations of all three major prototype calcium channel antagonists, nifedipine, diltiazem and verapamil, reduced lipid peroxidation in human low-density lipoproteins (LDL) as measured by the rate of formation of malondialdehyde in response to the generation of oxygen radicals[21]. Possibly lipophilic properties of certain agents such as amlodipine[24] and lacidipine may be important. An outstanding issue is whether these agents would have similar effects when given orally and chronically to patients. In the meantime it seems safe to conclude that laboratory antioxidant properties can be found with all calcium antagonists tested, but that the clinical relevance of these findings still remains uncertain.

**Antiplatelet effects**

Antiplatelet effects occur after oral administration of calcium channel antagonists to patients[25,26]. The mechanism may involve a lessening of cytosolic calcium response during platelet activation, and stimulation of the formation of nitric oxide, which in turn has anti-aggregatory effects[27]. These antiplatelet effects may account for the increased incidence of gastrointestinal haemorrhage recently found in a cohort study of elderly hypertensive subjects[28].

**Atheroma retardation**

The combination of antiplatelet effects, antioxidant properties, and endothelial protection should lead to decreased atheroma formation. Another mechanism would be through inhibition of the effects of established platelet-derived growth factor[19]. This, however, requires a supracellular concentration of verapamil of 10^-7 M to 10^-5 M. Calcium channel antagonists may lessen intimal proliferation, smooth muscle growth, smooth muscle migration, and cholesteryl ester formation at, in general, supratherapeutic concentrations[29].

Atheroma retardation has been clinically tested[30,31] with the conclusion that there is some effect on new plaque formation in coronary arteries as assessed by angiography. Nonetheless, from a clinical point of view, more impressive results have been found in the still unpublished results from longer term follow up of the INTACT study with nifedipine[30]. Of interest is the preliminary report that calcium channel antagonists may add to the effect of a statin in retarding coronary atherosclerosis independently of changes in total cholesterol[32].

**Graft arteriopathy**

The development of this very specific condition, found in post heart transplant patients, is counteracted by diltiazem[33].

**Regression of left ventricular hypertrophy**

In patients with angina and left ventricular hypertrophy, the oxygen demand is thought to be increased by the increased myocardial mass, and it is often thought that the capillary density is relatively decreased[34]. A present controversy is whether certain specific agents are better than others in regressing left ventricular hypertrophy. In one meta-analysis of 109 studies on 2357 patients, calcium channel antagonists reduced left ventricular hypertrophy mass by 10% whereas ACE inhibitors had a 16% reduction[35]. The single calcium channel antagonist most studied appears to be nifedipine and twice daily dosage of tablets appears to have been commonly used. Nonetheless, it is known that relatively short-acting dihydropyridines are not as effective in reducing left ventricular hypertrophy as expected, taking as example twice daily felodipine[36], presumably because of repetitive sympathetic activation. By contrast, in a study in which ultralong-acting nifedipine was used, left ventricular hypertrophy mass fell by 19% over 1 year[37,38] which is close to the percentage regression obtained with ACE inhibitors in the meta-analysis of Dahlof et al.[39]. At present it is a source of fierce debate whether calcium channel antagonists and ACE inhibitors are equally effective in achieving left ventricular hypertrophy regression; two prospective studies say 'yes'[37,38]. In experimental left ventricular hypertrophy, the rarefaction of capillaries that normally occurs is countered by nifedipine treatment, albeit in very high doses[39].

**Silent myocardial ischaemia**

In general, despite the conflicting data, the overall evidence suggests that all the major calcium channel antagonists can reduce the number of ST-segment deviations. In some of these studies, beta-blockers were more effective than calcium channel antagonists[40], and among the calcium channel antagonists, diltiazem might be more effective than short-acting nifedipine[41]. To obtain best results with the dihydropyridines, long-acting preparations may be needed such as nifedipine GITS[41] or Adalat-CC or amlodipine[42,43] or truly long-acting preparations of other drugs. There are no grounds for supposing that the silent episodes are caused by intermittent coronary artery spasm and/or that there is any specific role for calcium channel antagonists as opposed to beta-blockers. Thus far there are no outcome studies available concerning the use of calcium channel antagonists in silent ischaemia.

**Mixed or variable threshold angina**

Although the term 'mixed angina' has been widely used, the definitions have not been exact and the concept has become controversial. Ardissino et al.[44] defined 'mixed angina' simply as the co-existence of effort angina and rest angina, without any judgement as to the aetiology. For the present author, the latter definition seems simplest and clinically applicable. It also corresponds to the definition of variable threshold angina[40]. Other definitions have been reviewed. New knowledge that the ST-segment deviations found in patients with mixed
angina respond to therapy by beta-adrenergic blockade makes the vasospastic aetiology of such ECG changes questionable. A review of six existing trials shows that, in four, beta-blockade was preferable to therapy by short-acting nifedipine, while in the other two diltiazem was as effective as propranolol or atenolol. Therefore, mixed angina is not an automatic indication for therapy by calcium channel antagonists and, in fact, present evidence suggests preferential use of beta-blockers rather than short-acting nifedipine for such patients. Non-dihydropyridines, such as diltiazem or verapamil, may be preferred to dihydropyridines, but definite trial-based data are lacking.

**Transient rest angina**

Transient rest angina is here defined as repetitive short-lived anginal type chest pain at rest, less than 15 min in duration, without the features of true unstable angina, or a significant threat of imminent myocardial infarction, and differing in mechanism from true unstable angina. Of note is that true unstable angina carries with it the threat of evolution into acute myocardial infarction. Other definitions are considered elsewhere. In such transient angina at rest, the evidence for the benefit of all calcium channel antagonists is good. Furthermore, calcium channel antagonists are better than propranolol which may be ineffective. In contrast, when considering patients with true unstable angina (threat of myocardial infarction), nifedipine is less effective and in reality contraindicated as monotherapy and only benefits if accompanied by beta-adrenergic blockade.

Transient rest angina, as here defined, may only account for a small percentage (possibly about 6%) of all patients with chest pain. It is this apparently rather small group that is most likely to respond dramatically to calcium channel antagonist therapy. However, no long-term safety data for such therapy are available for these patients.

**Prinzmetal’s variant angina**

From the clinical point of view, a typical case of Prinzmetal’s angina with ECG ST-segment elevation during an attack of anginal pain at rest is often readily diagnosed. In such cases calcium channel antagonists rather than beta-blockers are standard therapy. The critical importance of separating off patients with Prinzmetal’s angina from true unstable angina at rest is shown by Gerstenblith et al. Patients already on propranolol were in addition given nifedipine or placebo; the difference favouring nifedipine was found specifically in those with ST-segment elevation (indicating Prinzmetal’s angina).

Although coronary spasm is the established cause of Prinzmetal’s angina, it should be remembered that Prinzmetal described the combination of ST-segment elevation during chest pain at rest in the presence of organic coronary artery disease. Thus, coronary angiography is often required to exclude underlying coronary artery disease which in the long run may respond better to interventional measures rather than to calcium channel antagonists. All calcium channel antagonists thus far tested are highly effective for true variant angina.
Possible role of coronary vasoconstriction (vasomotion) as a cause of or contributor to angina?

While major coronary spasm with Prinzmetal's angina is a clearly defined but rather rare condition, the more subtle features of lesser degrees of spasm may be much more common\[^{60}\]. At present there seems to be a role for coronary vasoconstriction, also called vasomotion, in producing nocturnal ischaemia\[^{62}\] in cold-induced angina\[^{63}\] and in hyperventilation-induced ischaemia\[^{64}\]. Even with coronary angiography, proof of the participation of vasoconstriction in rest angina is difficult to obtain unless ergonovine stimulation is used\[^{65}\]. In absolute terms, rather few patients with chest pain seem to have localized spasm as a dominant mechanism\[^{67}\].

Coronary vasoconstriction may also occur in effort angina\[^{65}\]. An important paper shows that exercise induces vasoconstriction of stenotic but dilatation of normal coronary artery segments and that nifedipine, a dihydropyridine, prevented such vasoconstriction\[^{66}\]. This condition, probably a common response to effort angina, should be distinguished from a Prinzmetal-type picture with ST-segment elevation induced by exercise, a condition that responds specifically to calcium channel antagonists\[^{69}\].

Early phase AMI

None of the calcium channel antagonists have been studied in detail in patients with early phase myocardial infarction, except for the adverse experience with nifedipine capsules in the first SPRINT study (Goldbourt \textit{et al.}, 1993\[^{66A}\]). Animal studies suggest a reduction in infarct size and in ventricular fibrillation. There is considerable experimental evidence that calcium channel antagonists should prevent early ventricular fibrillation resulting from ischaemia. The problem is how to balance this possible benefit against the negative inotropic effect\[^{67}\]. No clinical studies have attempted to use calcium channel antagonists to prevent early ischaemic ventricular fibrillation. A variety of agents have been given in the acute phase of myocardial infarction, including verapamil, nisoldipine, diltiazem, and nifedipine.

Nifedipine for early phase acute myocardial infarction

Nifedipine (10 mg sublingually) may induce haemodynamic improvements, such as an increase in cardiac output and a fall of a high wedge pressure, with a reduction in blood pressure\[^{68,69}\]. However, on formal testing nifedipine has shown no benefit in three large multicentre trials\[^{66A,70}\]. In two of these trials, patients randomized to nifedipine showed excess early but not late mortality\[^{56,66A}\]. Thus in the view of the present author, nifedipine is specifically contraindicated in early phase acute myocardial infarction.

In the giant TREN'T study, in which nearly 3000 patients were studied, nifedipine given as 10 mg four times daily for 28 days and started within 24 h of the onset of chest pain showed neither benefit nor harm. The TREN'T study also showed that patients on prior beta-blockade therapy had a reduced mortality, thereby reconfirming the benefits of beta-blockade as opposed to those of short-acting nifedipine. In yet another study\[^{72}\], 98 patients were randomized double-blind to nifedipine capsules 10 mg every 6 h, or placebo, with an average delay time of only 3-4 h after onset of chest pain. Treatment was continued for 52 h. No significant differences were found in clinical or enzyme parameters, and the mortality at 1 month was similar in both groups (nifedipine 10-9%, placebo 9-6%). All these studies show that there is no indication for routine use of short-acting nifedipine in acute or threatened myocardial infarction\[^{47,56,69}\]. The possible adverse effects of short-acting nifedipine in true unstable angina\[^{50}\] also strongly suggest that nifedipine in the absence of beta-blockade is not the therapy of choice in threatened myocardial infarction nor in actual acute myocardial infarction.

Verapamil or early phase acute myocardial infarction

In two studies\[^{73,74}\], verapamil apparently reduced parameters of myocardial infarct size when given intravenously and acutely. Clinical outcome data were, however, not reported. In a double-blind study of 217 patients\[^{75}\], verapamil 0.1 mg \textcdot} kg\textsuperscript{\textminus}1 intravenously (mean 4 h after onset of chest pain) followed by 120 mg three times daily did not reduce cumulative enzyme release. In a large, double-blind study on 1436 patients with acute myocardial infarction\[^{76}\], half were treated with verapamil starting with an intravenous dose followed by 120 mg three times daily; there was no difference in either acute or chronic mortality. More patients were withdrawn from the verapamil group than from the placebo group due to the development of second- and third-degree heart block. In addition, heart failure was more frequent in the verapamil-treated group. The single benefit of verapamil treatment was a reduction in intermittent atrial fibrillation. The second Danish study\[^{77}\] started verapamil later, 7-15 days after the onset of acute myocardial infarction. The results supported the concept that verapamil was beneficial in the postinfarct period provided that patients with overt heart failure were excluded. Retrospective and subgroup analyses of the two Danish studies\[^{76,77}\], a procedure open to possible criticism because of the different nature of the trials, suggest decreased reinfarction and mortality in the verapamil group when the late results are considered (22-180 days). In the first trial, the early adverse effects of verapamil might have balanced the later beneficial effects. By avoiding the early administration of...
Calcium antagonists and coronary disease

Mortality, all patients

Cardiac events

Cardiac events, heart failure

Cardiac events, no heart failure

0.5 1.0 1.5 2.0
Confidence limits

Figure 1. Cardiac events in MDPIT (diltiazem, open triangles) and DAVIT-II (verapamil, open circles) trials, showing confidence limits. Note that heart failure was differently defined in the two trials. Reproduced from [88] with permission.

verapamil[77], the dominant protective benefit of verapamil in the postinfarct period was shown. In a small trial that only studied 17 patients over 10 days, verapamil was ineffective in preventing early postinfarct angina and reinfarction[78], however, this report lacks data on the patients’ left ventricular function.

Diltiazem after onset of acute myocardial infarction

Diltiazem appears not to have been studied in any large series in the acute phase of the usual type of myocardial infarction with Q-wave development. In patients with non-Q wave myocardial infarction (formerly called non-transmural or subendocardial infarction), Gibson et al. have studied the effects of diltiazem started as 30 mg for the first dose, then 60 mg for the second dose within 24–72 h after the onset of infarction and then continued as 90 mg every 6 h up to 14 days. This regimen reduced the incidence of reinfarction and the frequency of refractory postinfarct angina without changing the low mortality[79]. However, the study suffers from four defects. First, the claimed statistical significance fades when the customary two-tailed t-test is used instead of the one-tailed test the authors preferred. Second, nearly two-thirds of the patients received beta-blockade, so that the real comparison was between diltiazem plus beta-blockade vs placebo plus beta-blockade. Third, the study was limited to very early reinfarction, within 14 days. There can therefore be no comparison with the beta-blocker studies in which mortality was reduced over a period of months and years. Fourth, the all-cause mortality was 3-1% in the placebo group and 3-8% in the diltiazem group (P=ns), with no trend to fall in the diltiazem group. Nonetheless, when taken together with similar patients in the DAVIT-II study, there was a significant 35% reduction in cardiac death or non-fatal reinfarction during the 12–18 month follow-up period[80].

Nisoldipine for early phase acute myocardial infarction

Wilson et al.[81] specifically studied the haemodynamic effects of this highly coronary vascular selective agent, given as 2–4 μg·kg⁻¹ intravenously. The haemodynamic effects were a fall in systemic vascular resistance, variable tachycardia, little or no change in the pulmonary wedge pressure, a decrease in arterial pressure, an unchanged rate-pressure product, and an increase in the ejection fraction. Because heart rate rose more than 15 beats·min⁻¹ in five of 24 patients with low-dose nisoldipine and six of 20 patients with high-dose nisoldipine, the Cape Town group concluded that nisoldipine was unsuitable for use in the acute phase of myocardial infarction.

Comparison of various calcium channel antagonists for acute myocardial infarction

Commerford[82] reviewed the experience in Cape Town with the use of nisoldipine, nifedipine (10 mg sublingually followed by 10 mg every 6 h for 24 h, with a total dose of 50 mg), tiapamil, and diltiazem in patients with acute myocardial infarction. A total of 103 patients was studied within 12 h after the onset of acute myocardial infarction. Although the designs of the trial were not the same and there was no randomization between the groups, there were, nevertheless,
similarities, particularly regarding patient characteristics and the methods of evaluation. Some conclusions could therefore be drawn about the different effects of the various agents. Nisoldipine and nifedipine, as expected, being potent vasodilators, were able to achieve rapid and effective reduction of the afterload as represented by the arterial blood pressure. The heart rate did not fall and in the case of nisoldipine increased significantly. Tiapamil and diltiazem reduced heart rate; nifedipine, tiapamil and diltiazem all reduced the rate-pressure product, and none of the agents had clinically significant negative inotropic effects. Nisoldipine, because of tachycardia, was potentially the most harmful of the agents studied. The overall conclusion was that of the agents studied, all save nisoldipine could be used with relative safety for a limited period in the acute stage of myocardial infarction when load reduction was required. If, in addition, an antiarrhythmic property were sought, then it would be logical to use agents such as verapamil and diltiazem. Verapamil congeners, such as gallopamil and mibefradil, should be considered for further clinical trials when reduction of the rate-pressure product is required by means other than beta-blockade in early phase acute myocardial infarction.

Ischaemic diastolic dysfunction

Background information would suggest that calcium channel antagonists should benefit ischaemic left ventricular dysfunction. First, the acute intravenous administration of verapamil and nifedipine to patients with coronary artery disease, and normal ejection fraction and contractility values improved indices of left ventricular diastolic dysfunction. Second, intravenous verapamil can substantially improve systolic parameters in similar patients; hence diastolic function must also have improved. Third, part of the response to treatment by verapamil or nicardipine in patients with chronic stable angina is improved diastolic function. Yet, in a careful recent study, verapamil given intravenously to patients with coronary artery disease and normal left ventricular function had mixed effects on diastolic indices. The time constant of relaxation, tau, was prolonged, whereas peak filling rates improved.

How are these apparent contradictions explained? A major point to consider is that non-invasive measurements of diastolic function, though useful, are complex in their execution and interpretation. For example, tau is dependent not only on the inherent rate of left ventricular relaxation but also on the pre- and afterload. Further, the effects of verapamil on left ventricular systolic and diastolic function are highly complex and sometimes conflicting. The degree of left ventricular ischaemia and its response to verapamil might vary. At a cellular level, an increased rate of uptake of calcium into the sarcoplasmic reticulum might theoretically be achieved by a normalization of calcium levels in cells previously overloaded by calcium. On the other hand, decreased entry of calcium through its channel, as a result of verapamil therapy, would automatically decrease the process of calcium-induced calcium release from the sarcoplasmic reticulum. This would lower cytosolic calcium levels but eventually run the risk of decreased uptake of calcium by the sarcoplasmic reticulum. An associated negative inotropic effect might increase left ventricular end-diastolic pressure, thereby increasing the preload and adversely altering the rate of relaxation. Therefore, the effects of verapamil and probably other calcium channel antagonists on ischaemic left ventricular diastolic dysfunction can generally be expected to be positive yet, to some extent, not fully predictable in the individual patient.

Postinfarct protection

Reinfarction and mortality

Much has been made of the fact that calcium channel antagonists as a group do not confer postinfarct protection according to a meta-analysis. Yet the overall data are skewed by inclusion of the two SPRINT (Secondary Prevention Reinfarction Israeli Nifedipine
Calcium antagonists and coronary disease

Table 1 Factors influencing myocardial oxygen balance in relation to angina pectoris

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Calcium antagonist category</th>
<th>Drug example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afterload reduction</td>
<td>All</td>
<td>All dihydropyridines and non-dihydropyridines</td>
</tr>
<tr>
<td>Blood pressure effect</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Aortic compliance</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td><strong>Negative inotropic</strong></td>
<td>Non-dihydropyridines</td>
<td>Verapamil, diltiazem (nifedipine, amlodipine)</td>
</tr>
<tr>
<td>Isotropic state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate reduction</td>
<td>Non-dihydropyridines</td>
<td>Verapamil, diltiazem</td>
</tr>
<tr>
<td>Counter-regulatory heart rate rise</td>
<td>Short-acting dihydropyridines</td>
<td>Nifedipine, nicardipine</td>
</tr>
<tr>
<td>No change</td>
<td>Ultralong-acting</td>
<td>Nifedipine-XL, amlodipine</td>
</tr>
<tr>
<td>Coronary vasodilation</td>
<td>Dihydropyridines</td>
<td>Nifedipine, nicardipine</td>
</tr>
<tr>
<td></td>
<td>(especially vascular</td>
<td>isradipine, felodipine, nicardipine&gt;</td>
</tr>
<tr>
<td></td>
<td>selective)</td>
<td>amlodipine= nifedipine</td>
</tr>
<tr>
<td>Vascular selectivity</td>
<td>Dihydropyridines</td>
<td>Weaker effect: verapamil= diltiazem</td>
</tr>
<tr>
<td></td>
<td>Verapamil-like agent</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>with T-channel effect</td>
<td>Mibefradil</td>
</tr>
<tr>
<td>Ischaemia selectivity</td>
<td>Vascular selective</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dihydropyridines</td>
<td>Nisoldipine</td>
</tr>
</tbody>
</table>

Trial post infarct trials which used rapidly acting nifedipine in a fixed dose and which were entirely negative[66A,88]. Of note, the second SPRINT study focused on high-risk patients and early administration of nifedipine capsules. In the nifedipine-treated group, there was an apparently increased mortality of 7-8 in the nifedipine group, vs 5-5 in the placebo group (odds ratio 1-60; 95% confidence intervals 0-86–3-00; not significant). The increased mortality was in the early phase, and the data are reminiscent of those of Muller et al[56], in early phase threatened myocardial infarction. Furthermore, the meta-analysis did not separately exclude patients with a history of prior heart failure, an important proviso built into the protocol of the DAVID-II trial[77,88]. Speculatively, had the nifedipine study been carried out with an ultralong-acting preparation, then reflex adrenergic activation might have been avoided with possibly a more favourable result.

**Post-infarct mechanical dysfunction**

The calcium channel antagonist gallopamil given to patients with uncomplicated first acute myocardial infarcts in good clinical condition (Killip Class I) was able to improve diastolic function of the heart as assessed by echocardiographic indices[89]. This was, however, only an acute study.

**The DEFIANT studies**[89A,89B]

In the first study, patients within 5 weeks of acute myocardial infarction and a mean ejection fraction which was modestly decreased at 42% but without overt heart failure, were randomized either to placebo (n=67) or to active treatment (n=68) by nisoldipine core coat preparation. After 4 weeks of double-blind treatment-there was a small improvement in left ventricular systolic

---

**Table 2 Morbidity and mortality during chronic therapy with long-acting calcium channel antagonists**

<table>
<thead>
<tr>
<th>Mortality study</th>
<th>Condition</th>
<th>Drug</th>
<th>CCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRAISE</td>
<td>CHF</td>
<td>Amlodipine</td>
<td>190/571</td>
<td>223/582</td>
</tr>
<tr>
<td>V-HeFT-III</td>
<td>CHF</td>
<td>Felodipine</td>
<td>31/224</td>
<td>29/227</td>
</tr>
<tr>
<td>DEFIANT-II</td>
<td>PMI</td>
<td>Nisoldipine</td>
<td>1/271</td>
<td>7/271</td>
</tr>
<tr>
<td>STONE</td>
<td>HTN</td>
<td>Nifedipine</td>
<td>15/817</td>
<td>26/815</td>
</tr>
</tbody>
</table>

CCA = calcium channel antagonist; CHF = congestive heart failure; PMI = postmyocardial infarction; HTN = hypertension.
function with, for example, an increase of 1% in the ejection fraction in the nisoldipine-treated group. Exercise capacity improved modestly. The largest changes found were in isovolumic relaxation, which increased during placebo treatment and decreased with nisoldipine. Thus, in post-infarct patients nisoldipine appeared to improve diastolic and to some extent systolic function. Two important points are that (1) the patients were not in overt heart failure and (2) the nisoldipine patients were on the whole 6 years younger than the placebo-treated patients, despite the randomization procedure. In the more recent DEFJANT-II study, similar results were obtained in a larger patient population, and there was no suggestion that nisoldipine increased mortality in this population group. In fact, the mortality in the group given nisoldipine was 1/271 versus 7/271 in the placebo group (difference not significant).

**DAVIT-II study**

DAVIT-II was not specifically focused on the problem of left ventricular post-infarct dysfunction. However, there are reasons to believe that diastolic dysfunction might have been present in the patients who benefited from verapamil. First, it needs emphasis that it was those patients without heart failure during their stay in the Coronary Care Unit who subsequently benefited from verapamil post-infarct; that benefit in the reduction of reinfarction and death was highly significant (P=0.008). Second, the majority of patients were in the same NYHA (New York Heart Association) category as in the DEFJANT study, namely category I. Third, a retrospective analysis showed that reduction of sudden death by verapamil was actually best demonstrated in patients with large hearts, indicating that there was some cardiac abnormality.

**Calcium antagonists and systolic heart failure**

Despite the strictures usually voiced against the use of calcium antagonists in systolic heart failure, carefully controlled studies are now being undertaken to define more precisely the possible role of calcium antagonist therapy in such patients.

**Nicardipine**

A preliminary report on 39 patients shows that nicardipine, which is a highly selective agent, improved ejection fraction and the duration of exercise in patients who stopped because of dyspnoea or fatigue. The benefits were found over 4 months of treatment. It must be stressed that these patients were not concurrently treated with ACE inhibitors as occurred, for example in the amlodipine trial.

**Nisoldipine**

This agent is even more vasoselective than nicardipine. Nisoldipine given to 12 patients over a period of 2-3 months reduced the peripheral vascular resistance, increased cardiac index, but did not change exercise tolerance. No clinical deterioration was found in these patients, although there was a small rise in the resting plasma norepinephrine levels.

Kiowski et al. showed that haemodynamic benefits could be sustained over 4 weeks of nisoldipine treatment in patients with congestive heart failure secondary to ischaemic or dilated cardiomyopathy. There were no adverse increases in plasma noradrenaline or renin levels.

In contrast, Barjon et al. found that nisoldipine given to 10 patients with congestive heart failure over 2 months led to clinical deterioration in seven of those patients. Although haemodynamic benefits were found after acute nisoldipine administration following on chronic therapy, when a water load was given over 5 h, nisoldipine decreased water excretion and increased plasma renin and plasma noradrenaline levels. The authors conclude that despite having beneficial haemodynamic effects, nisoldipine may increase neurohumoral stimulation and worsen the symptoms of congestive heart failure.

The differences between these two studies may lie in the presence of severe (Class III or IV) angina in the study by Barjon et al., whereas the patients of Kiowski et al. were free of angina. The form of nisoldipine (twice daily tablets) used in this study has been shown to be ineffective in angina and possibly to have adverse effects.

**Amlodipine**

In the PRAISE study (Prospective Amlodipine Survival Evaluation), the effects of amlodipine on survival in patients with Class III and Class IV heart failure were tested. A benefit of amlodipine was found in patients with clinical non-ischaemic cardiomyopathy, most of whom were also treated by ACE inhibitors. This agent may, therefore, be regarded as a possible addition to the diuretic-digoxin-ACE inhibitor therapy in severe congestive heart failure, clinically not ischaemic in origin.

**Felodipine**

In the V-HeFT III trial which compared long-acting felodipine with placebo on cardiovascular morbidity in 451 patients with Class II or more heart failure, this agent had no effect (i.e. neither harmful nor beneficial). In a smaller trial, extended release felodipine also gave neither benefit nor harm.
Combination of ACE inhibitor with calcium channel antagonist

If calcium channel antagonists in general exert adverse effects by peripheral vasodilation and stimulation of the renin-angiotensin system in patients with heart failure, then it is logical to suppose that their combination with ACE inhibitors should remove at least some of the adverse effects in systolic heart failure. Hypothetically, both haemodynamic and symptomatic improvement could be achieved. Whether or not this proposal is over-optimistic awaits further studies, particularly in postinfarct patients of the variety responding to verapamil or nisoldipine.

Vascular selectivity and heart failure

Thus far only the dihydropyridines have been tested for chronic effects in congestive heart failure. Some of these agents are much more vascular selective than verapamil or diltiazem. For example, nisoldipine is approximately 1000 times more vascular selective, felodipine and nicardipine about 100 times more, but amlodipine only 10 times more selective\textsuperscript{[94]}. Of interest is the finding that the most vascular selective of these agents, nisoldipine, is not obviously better in the management of heart failure than the much more modestly selective amlodipine. Although amlodipine and nifedipine are equally and modestly vascular selective, they appear to be very different in their effects in heart failure. Short-acting nifedipine is definitely contraindicated\textsuperscript{[101]}, and long-acting amlodipine shows benefits in selected patients. There may be many explanations for this difference, one being that short-acting nifedipine causes repetitive adrenergic stimulation, whereas long-acting amlodipine does not.

Long-term safety

An issue of recent concern is calcium antagonists' long-term safety in the presence of ischaemic heart disease\textsuperscript{[1,102,103]}. In the relatively small TIBET study, nifedipine tablets were as safe as atenolol in the long-term treatment of patients with chronic stable angina, with the same incidence of hard end-points which included unstable angina, myocardial infarction, and cardiac death\textsuperscript{[104]}. In post-acute myocardial infarction patients without clinical congestive heart failure, DAVIT-II showed that verapamil was safe and decreased re-infarction\textsuperscript{[88]}. In the recent CRIS (Calcium Antagonist Reinfarction Study\textsuperscript{[105]}), 1073 patients not receiving beta-blockers were randomized to verapamil 120 mg every 8 h, or to placebo, for 2 years. Death rates were unchanged, fewer patients developed angina, and there was a trend towards less reinfarction. Taking these data together with those of DAVIT-I and DAVIT-II, 15.2% of patients died or had reinfarction in the verapamil group, vs 17.1% in controls (odds ratio 0.86, 95% confidence intervals, 0.73 to 1.01) so that even more follow-up data are required to prove absolutely that verapamil confers postinfarct mortality protection\textsuperscript{[106]}.

In the APSIS study, verapamil over 3-4 years (median time) was as safe as metoprolol, as judged by the death rate, the incidence of acute myocardial infarction, severe angina, or a cerebrovascular incident\textsuperscript{[107]}. Despite these promising results, more long-term safety outcome studies on larger numbers of patients are required for calcium channel antagonists (and for \(\beta\)-blockers) in patients with effort angina.

References


events in patients with impaired cardiac function recovering from acute myocardial infarction. Eur Heart J 1993; 14: 540-5.


[98] Cohn J. Verbal presentation at the European Society of Cardiology Congress, Amsterdam, August 1995.