Left ventricular dysfunction: which role for calcium antagonists?

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Left ventricular dysfunction is the most common cause of congestive heart failure. Thus, treating or preventing left ventricular dysfunction represents an important therapeutic goal. The use of calcium antagonists in the treatment of left ventricular dysfunction or congestive heart failure has been proposed for many years now, mainly because of their potent vasodilatory effect. However, despite the theoretical basis, the results of studies exploring the possible use of calcium antagonists in this setting have not been at all encouraging. It has been suggested that this is because calcium antagonists have important additional effects: they depress cardiac contractility and activate the neurohormonal system.

The various calcium antagonists have different characteristics and can be potentially useful in a variety of clinical conditions. Amlodipine (a calcium antagonist with a minimal cardiodepressant effect, long half-life and minimal activity on the neurohormonal system) has been shown to be clinically useful in congestive heart failure of non-ischaemic origin.

Calcium antagonists capable of limiting heart rate increment are useful in limiting ischaemia-induced left ventricular dysfunction. Verapamil exerts a potent protective effect on both microvascular damage and mechanical recovery during prolonged ischaemia followed by reperfusion. Lastly, nisoldipine is capable of ameliorating left ventricular function in patients with left ventricular diastolic dysfunction and has, therefore, potential in the treatment of congestive heart failure of left ventricular diastolic dysfunction origin.

Thus, calcium antagonists may have a role in the treatment of left ventricular dysfunction provided that patient characteristics, the underlying mechanisms of the left ventricular dysfunction and the various calcium antagonist characteristics are well understood and carefully considered.

Key Words: Calcium antagonist, congestive heart failure, left ventricular dysfunction.

Introduction

Left ventricular dysfunction is the result of many cardiac disorders causing a mechanical alteration of cardiac performance. More importantly it can be the main cause of congestive heart failure. Given the clinical and prognostic impact of congestive heart failure, it is clear why much attention is paid to both the prevention and treatment of left ventricular dysfunction.

Left ventricular dysfunction can involve the entire left ventricle (overall left ventricular dysfunction) or only part of it (regional left ventricular dysfunction). The latter is particularly common in coronary artery disease, because of the regional nature of the disease and can, moreover, evolve into more severe overall left ventricular dysfunction and dilatation (left ventricular remodelling phenomenon).

Lastly, left ventricular dysfunction can be either systolic or diastolic, the latter being less uncommon than previously thought.

The role of calcium antagonists in the treatment of left ventricular dysfunction

Data so far on the use of calcium antagonists in left ventricular dysfunction, and more importantly in the treatment of congestive heart failure, its main consequence, have been somewhat conflicting. The question has recently become even more important, as it has been suggested on the basis of some meta-analyses that this category of drugs might even be dangerous.

Therefore, it seems worthwhile to review some important concepts and data that could be helpful in understanding the advantages, disadvantages,
Theoretical bases for the use of calcium antagonists for the treatment of congestive heart failure

An important effect of all calcium antagonists is their (more or less pronounced) vasodilatory effect. This is of great benefit in patients with congestive heart failure, in whom systemic vasoconstriction exerts a negative effect on cardiac performance. It has been thought that the beneficial effect of calcium antagonists might be even greater in patients with coronary artery disease, since they can have various forms of myocardial ischaemia that can cause worsening of regional left ventricular function. Calcium antagonists chiefly limit the extent and severity of myocardial ischaemia via reduced oxygen demand and augmented coronary blood flow. These relevant effects (reduction of systemic vascular resistance, limited extent of regional left ventricular dysfunction in the course of acute myocardial ischaemia, increased coronary blood flow) have favoured their use in the treatment of congestive heart failure, especially if it is of ischaemic origin. This is probably why, in the SOLVD Trial, calcium antagonists were found to be used in approximately 30% of cases with congestive heart failure.

The use of calcium antagonists in the treatment of congestive heart failure is further supported by studies demonstrating that they can exert a consistent beneficial effect on left ventricular function in experimental models of heart failure. This is the case, for example, in Syrian hamster cardiomyopathy induced by calcium overload and microvascular spasm.

Unfortunately, these theoretical considerations have not found the expected confirmation in experimental and clinical studies. Despite the expected vasodilatory effect no clinical benefit has been observed in a series of patients, whether in limited or in large trials.

Verapamil administration in patients with coronary artery disease and depressed left ventricular function further improves contractility when left ventricular ejection fraction is less than 30%\(^\text{1}\). Long-term therapy with diltiazem increases cardiovascular mortality and morbidity in patients with acute myocardial infarction and clinical signs of congestive heart failure\(^\text{1}\). Long-term administration of nifedipine, either alone or in combination with isosorbide dinitrate, in patients with mild to moderate chronic heart failure significantly worsened heart failure\(^\text{1}\).

The reason for the great discrepancy between theoretical considerations and clinical observations needs elucidation.

Why do calcium antagonists not exert a clinical benefit in patients with congestive heart failure?

The absent or, sometimes even deleterious effects of calcium antagonists in patients with congestive heart failure have been attributed to one or both of the following mechanisms: negative effect on myocardial contractility; neurohormonal activation.

Effect of calcium antagonists on myocardial contractility

Calcium antagonists’ negative effects on calcium transmembrane transport reduce myocardial contractility. This cardiodepressant effect has been thought to be the potential source of the observed negative clinical results. However, it has also been noticed that this depressant effect can be counterbalanced by peripheral vasodilation and especially by reflex sympathetic activation. This counterbalancing mechanical effect is, unfortunately, of little value in patients with congestive heart failure for two reasons. Firstly, intracellular delivery of calcium to the contractile apparatus is greatly impaired in patients with congestive heart failure\(^\text{3,6}\); thus, in these patients calcium antagonists may even further depress left ventricular contractility. Secondly, in patients with congestive heart failure, the capacity to respond to inotropic stimulus induced by sympathetic reflex activation is severely blunted. On these grounds the use of calcium antagonists should be avoided in patients with advanced forms of congestive heart failure, especially in conjunction with beta-blockers.

The cardiodepressant effect seems unlikely to be the explanation for these negative clinical results, since other drugs exerting a negative inotropic effect (such as beta-blockers) have shown a positive effect in the same clinical environment.

Calcium antagonists and neurohormonal activation

The neurohormonal system is activated by calcium antagonists in two different ways. In the first place, peripheral vasodilatation (however it is caused) is a well known stimulus for renin release; secondly, calcium exerts an inhibitory effect on renin release\(^\text{7-8}\). Hence calcium antagonists theoretically neutralize this inhibitory mechanism.

Activation of the renin-angiotensin system induces deleterious effects in patients with congestive heart failure. Vasoconstriction, salt and water retention occur when this system is activated; moreover, the renin-angiotensin system can bring about the development of complex ventricular arrhythmias. This is the result of potassium depletion that can occur because of the increased production of mineralocorticoids. All these
effects have, obviously, a very negative functional impact on patients with congestive heart failure. However, it is important to note that other treatments for congestive heart failure which can activate the renin-angiotensin system via vasodilatation (hydralazine, isosorbide dinitrate) have a positive clinical effect in patients with congestive heart failure\[9\]. This different effect suggests that drugs activating the neurohormonal system exert negative clinical effects in patients with congestive heart failure only when they are also capable of depressing myocardial contractility.

**Calcium antagonists in congestive heart failure: new approaches**

Calcium antagonists could be used for the treatment of congestive heart failure provided that particular conditions are met: (a) minimal inotropic effect on myocardium, or, better still no negative inotropic effects at all (b) a combination of calcium antagonists with ACE inhibitors to counterbalance the negative effects caused by neurohormonal activation, (c) the development of new calcium antagonists that do not activate the neurohormonal system.

Recent studies suggest that amlodipine, a second-generation dihydropyridine calcium antagonist, has functional and clinical benefits for patients with congestive heart failure. In a first multicentre, double-blind, placebo-controlled study it was shown that in patients with congestive heart failure treated with diuretics, ACE inhibitors and amlodipine, exercise time significantly improved, both at 4 and 8 weeks, in comparison to patients treated with placebo. Moreover, symptoms were also significantly improved in patients receiving amlodipine. Interestingly, these favourable functional and clinical findings were also associated with a significant reduction in plasma levels of norepinephrine\[10\]. These promising data, collected in a series of 118 patients, have found a more solid confirmation in the PRAISE trial. This involved 1153 patients with congestive heart failure of NYHA class II-IV\[1\]. Preclinical and improving coronary blood supply during ischaemia. It has been suggested that this beneficial effect was particularly evident when verapamil was administered before development of ischaemia or even at the time of reperfusion. This functional improvement may be due to a direct protective effect of verapamil on myocytes during both ischaemia and reperfusion and/or, as recently suggested, to protection of microvasculature and consequent reduction of the 'no reflow' phenomenon\[14\]. Experimental studies have shown that during ischaemia followed by reperfusion, microcirculatory damage occurs well before myocyte death develops\[15\]. In patients with recent myocardial infarction, preservation of microvasculature integrity and function guarantees viability as assessed by either functional recovery at follow-up or by contractile reserve at dobutamine stress echo-cardiography\[16-18\]. On the other hand, patients without adequate reperfusion, despite infarct-related artery re-opening after acute myocardial infarction ('no reflow phenomenon'), have a poor functional outcome after the acute event. Gallopamil and verapamil are capable of reducing the percentage extent of the no reflow phenomenon within the risk area after prolonged myocardial ischaemia. It has been suggested that this beneficial effect can be attributed to different mechanisms, including a possible antispastic effect on microvasculature\[14,19\]. This possible mechanism has been recently suggested by Piana and colleagues in a clinical study in which verapamil was successfully used to limit or abolish the no reflow phenomenon occurring after percutaneous transluminal coronary angioplasty\[20\].

**Effect of calcium antagonists on regional systolic dysfunction**

As previously mentioned, overall left ventricular dysfunction can be the result of adaptive evolution of a serious regional dysfunction. This condition is called 'left ventricular remodelling phenomena'. It mainly occurs in ischaemic heart disease since this can affect the left ventricle in a regional manner. Thus, it seems logical to attempt, when possible, a therapeutic approach aimed at limiting, if not even eliminating, the regional dysfunction, which is the main mechanism of progressive left ventricular enlargement. Calcium antagonists can play a very important role here, both in reducing the extent of dysfunctioning myocardium caused by myocardial ischaemia and in improving the functional recovery of post-ischaemic dysfunctional, but viable, myocardium.

Calcium antagonists, by reducing oxygen demand and improving coronary blood supply during ischaemia, exert a beneficial functional effect on left ventricular function in the course of acute myocardial ischaemia. In a study in which diltiazem was administered in patients with acute myocardial infarction undergoing exercise radionuclide angiography it was shown that both ejection fraction and regional wall motion score improved after calcium antagonist administration\[12\]. Verapamil administration in an ischaemia-reperfusion experimental model considerably improved both the degree and time course of recovery of post-ischaemic dysfunctional myocardium\[13\]. This beneficial effect was particularly evident when verapamil was administered before development of ischaemia or even at the time of reperfusion. This functional improvement may be due to a direct protective effect of verapamil on myocytes during both ischaemia and reperfusion and/or, as recently suggested, to protection of microvasculature and consequent reduction of the 'no reflow' phenomenon\[14\]. Experimental studies have shown that during ischaemia followed by reperfusion, microcirculatory damage occurs well before myocyte death develops\[15\].

**Effect of calcium antagonists on diastolic left ventricular dysfunction**

Congestive heart failure can be caused not only by systolic regional or global left ventricular dysfunction, but also by diastolic dysfunction. This last possibility is...
Calcium antagonists may have a role in the treatment of left ventricular dysfunction. The different characteristics of various calcium antagonists, as well as differences in pathophysiology of various forms of left ventricular dysfunction and congestive heart failure must be well understood and considered when treating the single patient.

Not all calcium antagonists can be given to all patients with left ventricular dysfunction or congestive heart failure. There are, however, specific clinical conditions in which calcium antagonists can be indicated and utilised. In established congestive heart failure a calcium antagonist with minimal cardiodepressant effect, long half life and exerting a minimal activation of neurohormonal system can be used. PRAISE trial results suggest that amlodipine meets these criteria and can be used in patients with congestive heart failure of non-ischaemic origin. However, calcium antagonists may also have a role in the early stage of congestive heart failure, when left ventricular diastolic dysfunction can be limited. Calcium antagonists limiting heart rate increments may have a role in left ventricular dysfunction of ischaemic origin. Verapamil has been shown to be effective in limiting the no reflow phenomenon after acute ischaemia and in ameliorating mechanical recovery. Thus, calcium antagonists may have a potential role in the very acute phase of myocardial infarction for a limited period time in patients in whom infarcted-related artery reopening has been successfully achieved by thrombolysis or percutaneous transluminal coronary angioplasty (PTCA). This hypothesis is currently being tested in a multicentre trial (VAMI: Verapamil in Acute Myocardial Infarction).

In this trial, patients with acute anterior myocardial infarction treated with thrombolysis within 4 h of chest pain onset are monitored over time by digital echocardiography. Digital echocardiograms are transmitted telephonically to a core laboratory for central reading.

Lastly, in some patients in whom left ventricular dysfunction of diastolic origin is present, nisoldipine could be potentially useful in ameliorating left ventricular dysfunction and in preventing further left ventricular deterioration.

Thus, accurate knowledge of patient history, the underlying mechanism of left ventricular dysfunction and pathophysiology are essential for optimum calcium antagonist administration in patients with left ventricular dysfunction.

References

Calcium antagonists in left ventricular dysfunction


