Why are Calcium Antagonists Still Being Used in Heart Failure in the Era of Calcium Sensitizers?

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Efficient treatment for dilated cardiomyopathy has become a challenge to research in heart failure. The high morbidity and mortality ratios with their consequent social impact, justify high levels of anxiety. In Brazil, 2 million patients have heart failure, and 240 thousand new cases appear every year. Approximately one third of these patients are hospitalized due to failure of compensation of the disease. The available therapeutic arsenal, including digitalis, diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers, has had less than expected effects on the natural history of congestive heart failure[1-5]. From the eighties onwards, popularization of calcium antagonists for the treatment of arterial hypertension and coronary disease resulted in the appearance of a great variety of drugs. Competition among pharmaceutical companies propelled research aimed at their greater clinical applicability. Despite unfavorable evidence, the use of calcium antagonists in cardiac failure is still widespread [6-8]. The paradox between scientific evidence and clinical practice was evident at the moment the first results suggesting the benefits of calcium agonists via sensitization of the binding of this cation to troponin C for the treatment of severe heart failure began to appear.

Theoretical background

Significant pharmacological differences exist between calcium antagonists, with regards to the intensity of action on myocytes, pacemaker cells, or vascular muscle, as well as to molecular mechanisms of action, degree of negative inotropism, and neuro-humoral activation [9-11]. Nevertheless, these drugs have systemic arterial and coronary vasodilator actions in common. Theoretically, a drug that could dilate the arteries, decreasing peripheral vascular resistance, could also reduce systolic parietal stress and consequently improve ventricular dysfunction in dilated cardiomyopathy [2,12].

The telesystolic pressure-volume curve in patients with cardiac failure became more horizontal. In these subjects, the use of arterial vasodilator drugs led to a small decrease in arterial pressure relative to the large increase in systolic volume. This model also substantiated the utilization of calcium antagonists in congestive heart failure [9]. Some experimental papers showed that calcium antagonists prevented the progress of heart failure [13,14].

Ischemic disease was the cause of heart failure in approximately 70% of the patients in 13 multicenter studies [4]. The known anti-ischemic and antihypertensive effects, as well as the action on diastolic dysfunction contributed to the utilization of calcium antagonists in heart failure [14,15].

Clinical and epidemiological motivation added to these theoretical bases through clinical research culminated in the results that will be analysed below.

Clinical results

Short-term studies that evaluated hemodynamic variables – Studies performed prior to the nineties investigated hemodynamic alterations produced by first generation calcium antagonists. They had methodological limitations like small samples, short periods of observation, exclusion of patients using other vasodilators, and absence of control groups [9]. Results had great variability, some patients showing improved cardiac output, but the majority of them showing a worsened hemodynamic picture including acute pulmonary edema and cardiogenic shock [9,16,17]. It would be difficult to attribute the differences in the results to pharmacological peculiarities of the various calcium antagonists used or to the heterogeneity of the populations studied. Results of study with long-acting dihydropyridines also showed disparities among the hemodynamic variables evaluated [16-20].

Studies of intermediate duration with observations on ergometric and hemodynamic variables – Reports from six studies of two to six month's duration, well organized and including control groups published between 1987 and 1995 are prominent. The effects of nifedipine, amlodipine, and felodipine showed divergent results. Parker et al [21] suggested a possibly beneficial effect of amlodipine on symptoms and increased tolerance to effort's. Regrettably,

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the authors were unable to categorically define the effects of calcium antagonists on exercise capacity and on the functional class of the patients with heart failure [21-26] (table I).

Long-term studies evaluating morbidity and mortality – Consonantly with the era of evidence-based medicine, better planned studies, with a greater number of participants, control groups, and longer follow-up periods became available. The first three of these [27-29] indirectly reported on the probable effect of calcium antagonists on heart failure, because in reality these studies were made to evaluate survival time in coronary disease immediately following acute myocardial infarction. The studies were limited because they worked with selected samples of ischemic patients. So, they were not representative of dilated cardiomyopathy in general. The analysis of patient subgroups with congestive heart failure revealed unfavorable results for the use of calcium antagonists (table II).

From 1996 on, other studies [30-33], reported the effects of calcium antagonists on morbidity and mortality ratios of congestive heart failure patients who were out of the set of acute myocardial infarction. None of these studies presented evidence significant enough to lead to a modification of the presently employed therapeutic conduct in cases of dilated cardiomyopathy. Only the PRAISE study [32] showed a significant reduction in morbidity and mortality ratios following the use of amlodipine in a nonischemic subgroup of patients, a result disagreeing with those reported for the long half-life dihydropyridines [34] (table III).

Blockade of T and L channels by Mibefradil – Theoretically the ideal calcium antagonist should be free of negative inotropic and neuro-humoral activating effects. Blockers like mibefradil acting predominantly on the T channel possess a lesser negative inotropic effect due to their preferential action on smooth vascular muscle and pacemaker cells. These drugs have a long half-life can be administered orally, and in studies in rats have shown to cause peripheral vasodilatation and decreased heart rate in the absence of neuro-humoral activation [35,36]. Experimental studies suggested, furthermore, that mibefradil reduced interstitial and perivascular fibrosis [37], protected myocardial calcium overload due to ischemia and increased beta-adrenergic responses in hearts with chronic failure [38]. The drug presented itself as a promising possibility for the treatment of heart failure. Its properties allied to intense advertising led it, within less than one year, to be used against systemic arterial hypertension by nearly 200 thousand patients in the United States of America. However, reports of serious adverse effects, some leading to death, attributed to the interaction of this calcium antagonist with at least 26 other drugs began to appear. Mibefradil inhibits the enzyme cytochrome P450 3A4, leading to potentiation of the effects of drugs like beta-blockers, digoxin, amiodarone, quinidine, lovastatin, simvastatin, and other calcium antagonists. These findings led the manufacturer to withdraw the drug from the market. It is most probable that from now on a more rigorous control of the release of new calcium antagonists will be exerted [39,40].

Calcium antagonists as antiarrhythmics in patients with heart failure - Digoxin is inefficient in the control of heart rate in atrial fibrillation in many patients with congestive heart failure, in particular in acute situations requiring fast action. This has led to the use of intravenous diltiazem as an alternative form of treatment. In the small number of cases studied, the drug has been shown to cause a rapid and efficient reduction in ventricular response in the absence of additional deterioration of ventricular function [41,42]. It is not known, however, what would be the intermediate- or long-term effects of this drug.

Consensual recommendations

Most recent publications of official organizations like

Table I – Studies of intermediate duration on ergometric and hemodynamic effects of calcium antagonists in heart failure

Study/ year	Design	n	Target population	Results
Tan et al[22] 1997	Felodipine x Placebo	15	ischemic; FC III	–↑CO at rest and at effort - Unchanged HR or ventricular pressure - No improvement of symptoms - ↑ Liquid retention
ElKayam et al[23] 1990	Nifedipine x Nitrate	28	FC II and III	- ↑ Hospitalizations - No compensation of HF - ↓ Adherence to therapy
Dunselman et al[24] 1990	Felodipine x Enalapril	20	FC III	- No alteration of duration of exercise no alteration of peak VO2 - ↓ HR and BP relative to Enalapril
Packer et al[21] 1991	Amlodipine x Placebo	18	FC II and FC III EF < 40%	- ↓ Symptoms - ↑ tolerance to effort
Littler et al[25] 1995	Felodipine x Placebo	252	FC II e III	- No differences between duration of physical effort in pre- and post phases of treatment
De Vries et al[26] 1995	Felodipine Enalapril	46	EF < 40%	- No differences in peak VO2 and tolerance to affort

CO- cardiac output; HR- heart rate; FC- functional class (New York Heart Association); HF-heart failure; V02 = oxygen consumption; BP- blood pressure; EF- ejected fraction.

Table II – Studies that evaluated the effect of calcium antagonists on the survival times of postinfarction patients

Study / year (Reference)	CA (daily dose) (mg)	n	Follow-up (months)	Target population (following AMI)	Results
MDPIT/[27] 1988	Diltiazem (240)	2466	25	3rd to 15th day shock and PAH	-No change in total mortality; - ↑ 414 relative risk relative to events in those with earlier HF
SPRINT/[28] 1988	Nifedipine (30)	2276	12	7 – 21 days - Moderate and severe HF excluded	- Unchanged mortality or re-infarct
DAVIT/[29] 1990	Verapamil (360)	1775	16	- 2nd week	- Unchanged morbidity and mortality in those with earlier HF

CA- calcium antagonist; AMI- acute myocardial infarct; PAH- pulmonary arterial hypertension; HF- heart failure.

Table III – Studies that evaluated the effect of calcium antagonists on the survival times of patients with congestive heart failure after the time of acute myocardial infarction

Study / year (Reference)	CA (daily dose) (mg)	n (months)	Follow-up (following AMI)	Target population	Results
DiDi /1996 (30)	Diltiazem (180-270)	186	24 < 50% CIn at rest and effort, PAP at effort, capacity for effort and symptoms	Dilated idiopathic Improved clinical parameters:	No change in mortality
PRAISE/1996 (32)	Amlodipine (10)	115	14 EF Ischemics and nonischemics	FC II and IV <30% ↓ 41% mortality in nonischemics	No change in morbility or mortality in ischemics;
V-HeFT III	Felodipine (10)	450	18 ischemic and > peripheral edema improved delayed	Males FC II and III	No change in morbidity and mortality; no difference between ischemics and nonischemics nonischemics Tendency towards

CA- calcium antagonist; EF-CA - calcium antagonist; EF - Ejection fraction; Cin- cardiac index; PAP- pulmonary arterial pressure; FC- functional class (New York Heart Association).

the Heart Failure Society of America [9], the Society of Cardiology of the State of Rio de Janeiro [3], the Society of Cardiology of the State of São Paulo [4], the Advisory Council to Improve Outcomes Nationwide in Heart Failure (USA) [43], and the Brazilian Society of Cardiology [5] counterindicate, with the possible exception of amlodipine, the use of calcium antagonists in heart failure.

Reevaluation of the theoretical background

Once the hypothesis of the beneficial effects of calcium antagonists in the treatment of heart failure has been disproved, it becomes necessary to return to its theoretical background to re-evaluate and to discuss the possible mechanisms of the adverse effects of these drugs. Katz [9] listed some explanations: 1) the vasodilator response to calcium antagonists at rest may not predict a similar response during exercise; 2) the vasodilator effect of these antagonists during exercise could divert blood flow from skeletal muscle to areas of low metabolism; and 3) clinical short- and long-term responses may reflect different pharmacological drug effects. An immediate action would be secondary to vasodilatation and the negative inotropic action, and the late effects would be related to the neuro-humoral response. Thus, the antagonist exhibiting the greatest neuro-humoral activity would tend towards greater clinical deterioration compared with the drugs not showing this effect. This would also explain why no increase in mortality was shown in studies where angiotensin converting enzyme inhibitors were also used. It is probable that the angiotensin-converting enzyme inhibitors blocked neuro-humoral activation by calcium antagonists.

Perspectives

Sensitizers of calcium binding to troponin C – The use of a sensitizer of the binding of calcium to cardiac troponin C has aroused considerable interest in the last three years. Levosimendan interacts directly with troponin C stabilizing contractile process proteins. Its action is directly proportional to calcium concentration; this makes it more efficient during systole, and it does not interfere with ventricular relaxation [44]. It has a potent predominantly venous vasodilator action attributed to the blockade of endothelin

1. The drug does not alter blood catecholamine levels. No tachyphylaxis was observed.

Levosimedan was initially applied by continuous infusion in patients with severe cardiac failure, dependent on intravenous inotropic agents. It caused hemodynamic improvement with increased cardiac output, decreased

pulmonary arterial pressure, and increased left ventricle ejection fraction. Reports of pilot studies showed that oral administration of the drug led to similar benefits, obviating, therefore, the interruption of the parenteral inotropic agents [44].

At therapeutic doses, no increase in heart rate or QT interval in continuous 24-h electrocardiography was noted. However, higher doses produced mild tachycardia and increase of the corrected QT interval. No episodes of nonsustained ventricular tachycardia, new supraventricular, or ventricular arrhythmias were observed in the 386 patients studied [44].

Results of the LIDO study were recently presented at the III Meeting of the Heart Failure Society of America [45]. In this double blind, randomized study, performed on 203 patients with noncompensated heart failure in 40 European centers, the effects of intravenous levosimedan were compared with those of dobutamine. Regarding hemodynamic variables, 28% of the levosimedan group attained the primary end point of a ≥30% increased cardiac index versus 15% in the dobutamine group, and a ≥25% reduction of wedge capillary pulmonary pressure. One hundred and eighty day mortality was smaller in the levosimendan group (0.57 relative risk, confidence interval at 95%, 0.34 to 0.95, with p=0.029). Collateral effects like tachycardia, angina pectoris, and rhythm disturbances were more frequent in the dobutamine group (11 to 5%).

Inflammatory cytokines and calcium antagonism – It has been established that pro-inflammatory cytokines depress myocardial contractility and intracellular calcium currents in heart failure [46]. Cytokines cause increased production of nitric oxide by induction of nitric oxide synthase, leading to a negative inotropic effect. Amlodipine in vitro decreased nitric oxide overproduction in an experimental model of heart failure of nonischemic etiology [47]. It is possible that this mechanism explains the beneficial results obtained with amlodipine in a subgroup of nonischemic patients in the PRAISE study [31,32].

Phospholamban, a regulatory protein acting on calcium-ATPase, may be implicated as the mediator of myocardial depression induced by cytokines. The expression of phospholamban has been experimentally induced by the transference of adenovirus genes [48].

New calcium antagonists - New dihydropyridines have been studied in Japan, initially aiming at the treatment of arterial hypertension. Cilnidipine led to vasodilatation without inducing reflex tachycardia, acting on the L and N channels (neuronal) [49]. Cilnidipine produced hemodynamic improvement without leading to sympathetic stimulation in experimental models, probably because of its N-channel blocking activity [50,51].

Bay y 5959 is another drug with antagonistic (it increases the inactivation ratio) and calcium agonistic effects (it increases the mean time for the opening of calcium channels). The drug had a positive inotropic effect, produced without alteration of vascular tone, heart rate or automatism [52].

Final considerations

No doubt remains that in the face of presently available evidence, first generation calcium antagonists are not indicated for patients with heart failure, even if ischemic or hypertensive etiology. This counterindication does not apply in the specific case of amlodipine whose use, however, does not offer great advantages.

It is difficult to define whether the use of calcium antagonists in heart failure reflects the high prevalence of ischemic and hypertensive cases of dilated cardiopathies in developed countries or is a consequence of the influence of the pharmaceutical industry on medical prescriptions. It is worth questioning the influence of the results of large clinical trials on current medical practice.

Recent results with levosimendan lead us to consider whether we are in a transitional phase between using calcium antagonists and calcium agonists as methods for treating heart failure. The return to basic research aimed at the elucidation of cell and molecular mechanisms of cardiomyopathies, calcium metabolism, and the actions of calcium antagonists may perhaps bring answers to these many questions and aid in the development of a much sought after therapy to modify the natural history of heart failure.

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