

Effects of calcium antagonists on hypertension and diastolic function

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Summary

Calcium antagonists are known to decrease blood pressure acutely and chronically in hypertensive patients with hypertensive heart disease, and also to improve their systolic function. However, disorders of diastolic function may occur early in hypertensive heart disease. The improvement of diastolic function by nifedipine and diltiazem is described, although it was difficult to exclude systolic unloading as a cause of the improvement. It is emphasised that diastolic dysfunction can exist in hypertensive heart disease, and that the calcium antagonists nifedipine and diltiazem can improve diastolic dysfunction.

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Abnormalities of diastolic function are now known to be a very sensitive indicator of myocardial functional abnormalities, sometimes being detected before there are systolic abnormalities.^{1,2} In patients with hypertension, in the early phases the ejection fraction is frequently normal or high, whereas diastolic relaxation may be impaired.^{3,4} Such diastolic dysfunction with impaired left ventricular (LV) filling may theoretically explain the early occurrence of exertional dyspnoea even at a stage when patients still have normal systolic function as shown by a normal ejection fraction.

Experience with calcium antagonism by nifedipine and diltiazem when given acutely to patients with hypertension is reported and the data compared with other published studies. It is argued that normalisation of early diastolic dysfunction is a desirable therapeutic aim.

Subjects and methods

For studies with nifedipine, 13 patients with an increased cardiothoracic ratio on straight postero-anterior chest radiography were studied. Criteria for selection were similar to the 37 different patients studied only for ejection fraction by Jennings *et al.*⁵ Measurements were made before and 20 minutes after 10 mg nifedipine given sublingually. For studies with diltiazem, a similar group of 11 patients (2 the same as in the nifedipine study) was chosen (mean age 59 years, 7 women, 4 men). Measurements were made 60 minutes after administration of oral diltiazem 90 - 120 mg (60 mg to 1 patient, 90 mg to 6 patients, 120 mg to 4 patients; mean dose 98 mg). The method of assessment of diastolic function by equilibrated radionuclide angiography was similar to that used by Lavine *et al.*⁶ and Inouye *et al.*²

Statistical analysis. Values are expressed as mean \pm SEM. Student's *t*-test for paired comparisons was used with two-tailed *P* values.

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Results

The results are summarised in Tables I and II and Figs 1 and 2. The acute blood pressure changes during the administration of nifedipine together with changes in the ejection fraction have already been published elsewhere.⁵ The chief findings of note were as follows: nifedipine, in addition to reducing systolic and diastolic blood pressure and slightly enhancing the ejection fraction, also increased the average diastolic filling rate (Fig. 1). There were no changes in the time to the peak filling rate, nor in indices of systolic phase function such as peak systolic ejection rate or mean systolic ejection rate. With diltiazem the blood pressure decreased (Fig. 2) during the period of observation, with the first systolic decrease occurring at 30 minutes (borderline statistical significance); 50 minutes was required for the diastolic and the systolic pressures to reach statistical significance by when they had fallen from initial systolic values of $187 \pm 8,6$ mmHg (means \pm SEM; *N* = 11) to $161 \pm 7,3$ mmHg, while the fall in diastolic values was from $117 \pm 5,2$ mmHg to $102 \pm 6,0$ mmHg (*P* < 0,01 systolic; *P* < 0,05 diastolic). Diltiazem also increased the ejection fraction (Fig. 3) and the peak diastolic filling rate, while leaving the indices of systolic function unchanged (Table II).

For comparison the effects of diltiazem on a group of 7 patients with hypertrophic cardiomyopathy were also studied (Table III). There were no changes in the ejection fraction (control 76%), or in the heart rate (control 76/min), or in the time to peak filling rate (0,35 s). However, with diltiazem the peak diastolic filling rate rose from $2,67 \pm 0,39$ end diastolic volume (EDV)/s to $3,30 \pm 0,33$ EDV/s (*P* < 0,01). Average diastolic filling rates were marginally increased from $1,24 \pm 0,16$ EDV/s to $1,40 \pm 0,15$ EDV/s (borderline NS, *P* value 0,06).

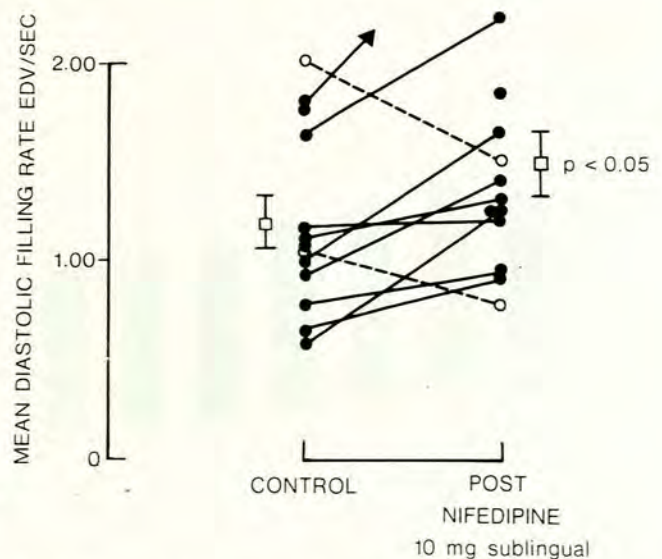


Fig. 1. Effect of nifedipine on diastolic filling rate. Post-nifedipine studies were conducted 20 minutes after 10 mg sublingual nifedipine.

TABLE I. NIFEDIPINE AND RADIONUCLIDE INDICES OF LV SYSTOLIC AND DIASTOLIC FUNCTION IN HYPERTENSION (N = 13)

	Pre-nifedipine	Post-nifedipine	P values
Ejection fraction (%)	64,8 ± 2,9	67,6 ± 3,2	<0,03
Blood pressure (mmHg)*	182/113 ± 5/3	162/99 ± 4/3	<0,003
Heart rate (/min)	76,3 ± 4,8	82,5 ± 3,5	NS
Peak systolic ejection rate (EDV/s)	3,27 ± 0,21	3,66 ± 0,27	NS
Mean systolic ejection rate (EDV/s)	1,94 ± 0,16	1,98 ± 0,14	NS
Time to peak filling rate (s)	0,34 ± 0,01	0,35 ± 0,01	NS
Peak diastolic filling rate†	2,79 ± 0,20	3,05 ± 0,31	NS
Mean diastolic filling rate†	1,19 ± 0,13	1,48 ± 0,16	<0,05

* From a similar but not identical group of patients (Jennings *et al.*)
 † EDV/s 30 minutes after nifedipine 10 mg sublingually.

TABLE II. DILTIAZEM AND RADIONUCLIDE INDICES OF LV SYSTOLIC AND DIASTOLIC FUNCTION IN HYPERTENSION (N = 11)

	Pre-diltiazem	Post-diltiazem	P values
Ejection fraction (%)	60,4 ± 4,5	65,9 ± 4,1	<0,01
Blood pressure (mmHg)	187/117 ± 9/13	161/102 ± 7/6	<0,05
Heart rate (/min)	62,7 ± 2,9	61,4 ± 2,9	NS
Peak systolic ejection rate (EDV/s)	2,64 ± 0,32	2,83 ± 0,31	NS
Mean systolic ejection rate (EDV/s)	1,67 ± 0,15	1,79 ± 0,18	NS
Time to peak filling rate (s)	0,36 ± 0,12	0,36 ± 0,10	NS
Peak diastolic filling rate*	2,48 ± 0,21	2,72 ± 0,23	NS
Mean diastolic filling rate*	0,95 ± 0,10	1,01 ± 0,11	<0,05

* EDV/s Post-diltiazem = 50-60 min after oral diltiazem, mean about 100 mg.

TABLE III. NIFEDIPINE AND HYPERTROPHIC CARDIOMYOPATHY

	Pre-nifedipine	Post-nifedipine	P values
Fractional shortening (%)	45	47	NS
Heart rate (/min)	71	78	<0,001
Isovolumic relaxation time (ms)	112	83	<0,001
LV filling (mm/s)*	72	101	<0,01

* LV internal dimension increase 20 min after 10 mg sublingual nifedipine.
 Data extracted from Lorell *et al.*¹⁶ with permission.

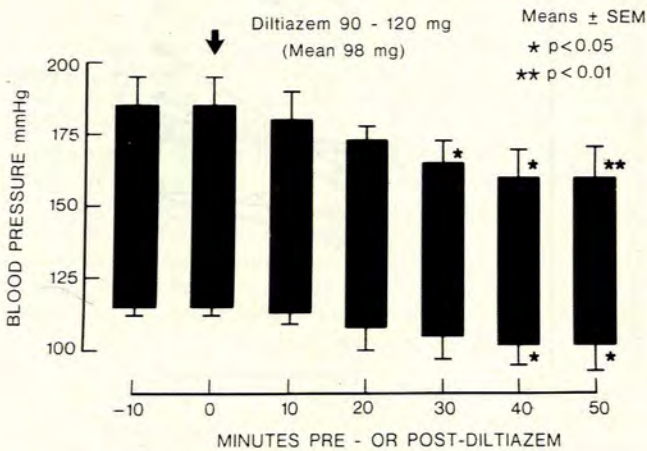


Fig. 2. Effect of diltiazem on arterial blood pressure after an acute dose (90-120 mg diltiazem, average 98 mg). Note that at time of blood pressure fall at 50 minutes post-diltiazem, both the systolic and diastolic functions of the myocardium improved (Table II).

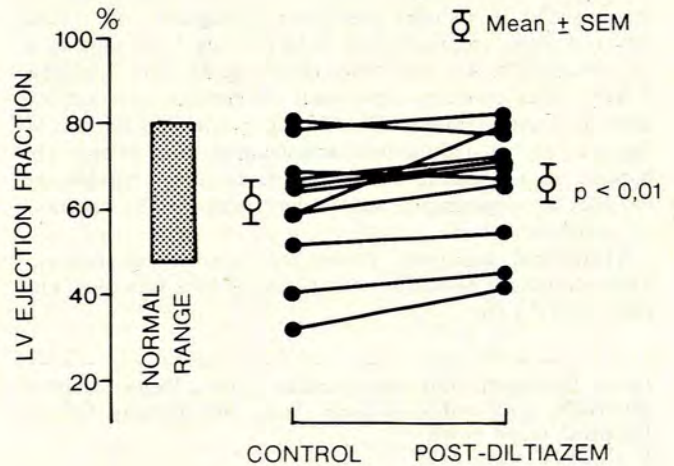


Fig. 3. Effect of diltiazem on LV ejection fraction 50-60 minutes after acute oral dose of 90-120 mg (mean, 98 mg).

Discussion

Diastolic abnormalities in hypertension

Diastolic abnormalities are now accepted as a well established complication of hypertensive heart disease. The new aspect of the present report is the finding that nifedipine given sublingually improves diastolic filling within 20 minutes and that diltiazem given orally does likewise within 60 minutes. These findings may be interpreted in relation to the role of other abnormalities of LV function in hypertension, as well as a consideration of the role of LV hypertrophy in the genesis of such altered diastolic function.

In hypertensive heart disease, there may be abnormalities of all phases of diastolic function, with slowing of early isovolumic relaxation, decreased early filling, prolonged late filling, and an increased atrial contraction phase.⁷ Such abnormalities have been shown by a variety of methods including echocardiography,^{3,7} radionuclide equilibrated angiography^{2,4} and Doppler echocardiography.⁸ The abnormalities of diastolic function correlate well with the increase of LV mass² and may be detected before there is definite evidence of systolic cardiac impairment.^{1,3} However, isolated patients have been reported in whom abnormalities of diastolic function have been found even when not accompanied by an increased LV mass as measured by echocardiography.⁹

Diastolic function in other causes of hypertrophy

An important question is whether the abnormalities of LV diastolic function are specific to hypertension or whether they merely indicate LV pressure overload. In the latter case similar abnormalities would be expected in patients with aortic stenosis. Some studies suggest that the echocardiographic abnormalities of diastolic function are similar in patients with hypertrophic cardiomyopathy or aortic stenosis,⁶ hypertrophic cardiomyopathy, and LV hypertrophy of systemic hypertension.^{8,10} Hanrath *et al.*⁷ were able to show some differences in diastolic function between hypertrophic cardiomyopathy and hypertensive hypertrophy, with an increased atrial 'booster' effect compensating better for the abnormalities of the pressure overloaded state. None the less these authors were unable to make any clear distinction between these conditions and the findings in the one blended into those in the other. Furthermore, as they point out, it is difficult to exclude minor degrees of ischaemia in severe hypertrophic cardiomyopathy and ischaemia could cause delayed LV relaxation. Spirito *et al.*¹¹ found an overall link between ventricular hypertrophy in hypertrophic cardiomyopathy, and abnormal diastolic function, yet in some non-hypertrophied myocardial segments, there were also abnormalities of diastolic function. Thus the links are not absolute and the genesis of the impaired LV relaxation may be multifactorial in origin and not only related to the degree of LV hypertrophy.¹² The cause of the hypertrophy seems to be important in determining the abnormalities of LV diastolic function. In *athletes* an increased LV mass is associated with normal diastolic function.^{3,13} Hence these data in man accord with animal experiments which suggest that exercise-induced hypertrophy might be 'better' than diseased-induced hypertrophy from the point of view of myocardial function.¹⁴

Role of calcium antagonist agents in LV hypertrophy

Initial studies were in severe hypertrophic cardiomyopathy. Hanrath *et al.*⁷ administered intravenous verapamil and found a decrease in LV isovolumic relaxation time. Chatterjee *et al.*¹⁵ reviewed the effect of calcium antagonist agents on diastolic

function in hypertrophic cardiomyopathy, arguing for an overall benefit on both systolic and diastolic function. Nifedipine 10 mg sublingually given to patients with hypertrophic cardiomyopathy improved isovolumic relaxation time and LV filling,¹⁶ yet it is difficult to be sure that the improvements were not a reflection of the increased heart rate. Hence our data on hypertrophic cardiomyopathy are of interest because diltiazem improved diastolic function while not changing the heart rate.

Similar beneficial effects of calcium antagonists have been described in hypertensive patients following nitrendipine⁴ which reverted diastolic abnormalities towards normal. It should, however, be noted that they used the same control groups in Tables I and II of their study, therefore invoking multiple comparisons which should have been corrected by the Bonferroni method,¹⁷ thereby weakening the statistical strength of their findings. In contrast, Inouye *et al.*¹⁸ found that 4 weeks of chronic treatment with diltiazem did not alter the peak diastolic filling rate nor the first third filling time, although 7/10 patients improved as far as the latter parameter is concerned. It is possible that the wide errors inherent in the radionuclide methodology might have obscured a benefit over 4 weeks of treatment. From that point of view we feel that our acute study, repeated in the same patients early after a single dose of nifedipine (20 minutes) or diltiazem (60 minutes) was designed to show up relatively fine differences. Thus our data agree with the concept that there are diastolic abnormalities in hypertensive heart disease and that the use of calcium antagonist agents may help revert these abnormalities towards normal.

It might be argued that the acute hypotensive effect of diltiazem and of nifedipine might have improved systolic function which in turn could alter diastolic function which is in part dependent on systolic loading.¹⁹ Fouad *et al.*²⁰ showed that in hypertensive patients the maximum filling rate improved as the maximal ejection velocity increased; however, the increase was much less in hypertensives than in normals. A decreased afterload, by reducing systolic loading conditions, might also have improved early diastolic function.¹⁹ We therefore had no proof of a specific effect of nifedipine nor of diltiazem on diastolic function in our hypertensive patients, as systolic unloading could theoretically explain the improved diastolic function. However, in our patients with hypertrophic cardiomyopathy, improved diastolic function was found in the absence of any increase in LV ejection fraction or change in heart rate or blood pressure.

LV mass — the crucial link

LV hypertrophy may impair diastolic function.^{1,2} Even though the link between myocardial hypertrophy and diastolic abnormalities are not absolutely tight,^{9,11} none the less there is a good overall correlation. Hence it is important that the chronic use of calcium antagonists including nifedipine, verapamil and diltiazem has been shown to decrease LV mass in hypertensive patients.^{21,22} In the case of nifedipine, a decreased cardiothoracic ratio has been reported during chronic therapy in combination with β -blockade and diuretics.²³ Because an increased LV mass is associated with diastolic functional abnormalities,² it may therefore be expected that the acute benefit on diastolic function found in our study may be translated into sustained benefit during prolonged nifedipine therapy. However, proof of this attractive hypothesis is presently lacking.

An important reservation to our study is that we did not show that therapy with calcium antagonists was able to relieve dyspnoea in the presence of normal systolic function. Such exertional dyspnoea is presumably caused by diastolic dysfunction and should improve with calcium antagonist therapy. This proposal should also be the subject of further clinical

trials. However, an important possibly relevant finding is that in ischaemic heart disease, diastolic dysfunction relates to exercise and tolerance independently of changes in systolic function.²⁴

Nifedipine v. other calcium antagonists

Calcium antagonists are now established antihypertensive agents. Nifedipine is among the best studied for its anti-hypertensive effect, and it induces hypotension after 20-30 minutes of sublingual administration, accompanied by improved systolic⁵ and diastolic function (present data) in our patients with radiologic cardiomegaly. A similar degree of hypotension was observed after 50-60 minutes following oral diltiazem in our patients. In the case of oral verapamil, 60 minutes is also likely to be required for the acute hypotensive effect.²⁵ The difference between the onset of action of nifedipine and other agents is therefore 30 minutes or more, which can be of crucial practical significance when testing the acute hypotensive response to a calcium antagonist in the doctor's consulting room.^{5,23}

While no differences could be detected in our acute study between the effects on diastolic function of nifedipine and diltiazem, it should be kept in mind that patients with complicated hypertension are frequently already receiving pre-existing therapy when referred for specialised opinion. Nifedipine may safely be combined with pre-existing β -blockade even when the ejection fraction on β -blockade is low (mean 32% in 4 patients, increasing to 38% after nifedipine²³). Haemodynamically, nifedipine is easier to combine with β -blockade than is verapamil or diltiazem because there is less chance of an increase in end-diastolic volume or prolonged PR-interval as shown in patients with ischaemic heart disease;²⁶ similar principles should hold for hypertensive patients. In animal experiments, the combination of nifedipine with β -blockade caused no change in ventricular relaxation, whereas the time constant was prolonged by the combination β -blockade-verapamil.²⁷

Reservations

It should be pointed out that: (i) the nifedipine data on blood pressure measurements presented in Table I were obtained from a different study;⁵ (ii) sublingual and not oral nifedipine was used; and (iii) the diastolic data in Table I were collected 30 minutes after nifedipine administration and not at 20 minutes as were the other data. The use of sublingual nifedipine in this study can be criticised because of erratic and poor absorption.²⁸ However, it should be borne in mind that in their study after the nifedipine capsule was bitten, the contents were held in the mouth for 20 minutes before being swallowed. In normal clinical practice, biting the capsule is inevitably followed by swallowing at least some of the liquid contents. In our study on a total of 80 patients,⁵ a consistent hypotensive effect lasting for 20-40 minutes²⁹ was obtained after sublingual nifedipine. Although the omission of blood pressure measurements in the present study could be criticised, the consistent effect in previous studies on 80 patients⁵ together with an increase of the ejection fraction similar in magnitude to that previously found, as well as the improved diastolic function, all suggest that nifedipine given sublingually was active in the present study. Because of the prolonged hypotensive effect of nifedipine given sublingually,²⁹ the discrepancy between the studies done at 30 minutes after nifedipine (diastolic function) and those done at 20 minutes (systolic function) would appear not to be serious. None the less, such discrepancies in the timing should be considered if precise interpretation of the timing of the data is crucial.

Clinical application

Diastolic dysfunction in hypertension may present as impaired left ventricular filling with exertional dyspnoea and pulmonary congestion. Besides diuretics, calcium antagonists (usually contraindicated in congestive heart failure with major systolic dysfunction) may be used to decrease blood pressure and improve myocardial function. Digitalis compounds such as digoxin are not appropriate therapy for diastolic dysfunction and should be avoided.

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