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Effects of Unloading and Positive Inotropic Interventions on Left Ventricular Function in Asymptomatic Patients with Chronic Severe Aortic Insufficiency

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Summary: The effect of an unloading (nifedipine, 20 mg sublingually) and of a combined unloading and positive inotropic intervention (nifedipine plus digoxin, 0.5 mg intravenously) on left ventricular performance was assessed in 48 patients with chronic severe aortic insufficiency. The left ventricular pump function-myocardial contractility relation (ejection fraction, EF vs. peak arterial pressure to end-systolic volume ratio, PAP/ESV), and the pump function-afterload relation (EF vs. mean systolic wall stress, MWS) were constructed by means of quantitative M-mode and two-dimensional echocardiography. In patients with normal control pump function (n=14), nifedipine markedly decreased MWS, moving the patients to a new, more advantageous EF-MWS relation. In the 34 patients with abnormal pump function, the myocardial contractility level was the mean factor conditioning the response to pharmacological intervention. Patients with a value of PAP/ESV greater than 2.5 (n=22) had normalization of EF after nifedipine and were upgraded to a more advantageous outlook for left ventricular mechanics EF-MWS and EF-PAP/ESV relations. Of the 12 patients without normalization of EF after nifedipine, only the 4 patients with PAP/ESV greater than 2 had normalization of pump function indices after combined administration of nifedipine and digoxin.

Key words: aortic insufficiency, quantitative echocardiography, left ventricular function, unloading agents, positive inotropic agents

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Introduction

The natural history of asymptomatic patients with severe chronic aortic insufficiency (AI) is influenced by two main factors: an early increase of left ventricular (LV) wall stress and a late depression of myocardial contractility. It is well recognized that irreversible structural and functional damage of LV muscle can develop even if patients do not experience significant symptoms. Such damage could preclude a good surgical outcome but precise guidelines regarding the timing of surgery are not yet available, and the prevention of myocardial dysfunction remains a fundamental unresolved clinical problem.

The loss of cardiac cells, fibrosis, and cavity dilation with "plastic change" have been recognized as irreversible myocardial lesions.[1] In chronically overloaded left ventricle, the irreversible lesions are due to the metabolic and mechanical changes determining a condition of increased total energy expenditure and decreased myocardial efficiency.[2] Recently, the importance of the underperfused subendocardium causing a self-perpetuating process[3] and the potential role of microvascular spasm as causes of irreversible myocardial lesions have been stressed.[1] Thus, particular attention must be paid to the drugs unloading the left ventricle and preserving coronary blood flow in the early treatment of asymptomatic patients with AI.

In order to contribute to a rational approach for the therapy of these patients, we studied the pattern of LV function after administration of digoxin, a traditional positive inotropic drug, and nifedipine, a calcium-channel blocker whose net hemodynamic action is the result of a complex interplay of simultaneous modifications in ventricular preload, afterload, and coronary blood flow.[4,5]

Material and Methods

Patients

The study group included 48 patients (40 males and 8 females with a mean age of 36 years; range 22-52) with chronic isolated severe aortic insufficiency. Severe AI was

quantified by a hemodynamic study in 34 patients and by cardiac flow Doppler echocardiography in 14 patients. None of the patients had an aortic pressure gradient greater than 20 mmHg. All patients older than 40 years were submitted to coronary arteriogram; none of them had critical stenosis (greater than 50%). All patients were asymptomatic. All therapy with cardioactive medications was tapered gradually and withdrawn completely before introducing a patient into the study program.

Based on their control echocardiographic pattern of LV function and response to the pharmacological interventions, the study patients were divided into three groups: Group A consisted of 14 patients with normal LV systolic shortening indices (ejection fraction greater than 60%, fractional shortening greater than 29%). Of the remaining 34 patients with abnormal control values of systolic shortening indices, 22 (Group B) had normalization after nifedipine administration and 12 (Group C) maintained an abnormal value of LV systolic shortening indices after the unloading agent.

Study Program

The 48 study patients had an acute test with nifedipine after a control echocardiographic examination of LV function: 20 mg of nifedipine were administered by opening the fluid-filled capsules and applying the contents beneath the tongue; the subject was instructed to retain the solution sublingually for as long as possible without swallowing. After 30 minutes, at which time the full nifedipine effect was observed,[6] an echocardiogram of the left ventricle was repeated.

In Group C patients, nifedipine (20 mg sublingually) and digoxin (0.5 mg intravenously) were administered simultaneously after the disappearance of nifedipine action on LV function and the return to control values of systolic arterial pressure: echocardiograms were recorded after 15, 30, and 45 minutes. During the study the heart rate was monitored by an electrocardiographic tracing and the arterial pressure was recorded by mercury sphygmomanometry simultaneously with the echocardiographic examination of LV cavity dimensions.

Echocardiographic Study and Analysis

Two-dimensional and two-dimensional-guided M-mode echocardiograms of the left ventricle were recorded at rest and under each experimental condition with a Hewlett-Packard phased-array ultrasonoscope and a 2.5 or 3.5 MHz transducer. An electrocardiogram (lead II) and blood pressure were recorded at the time of each echocardiographic study. M-mode left ventricular dimensions, posterior wall and septal thickness were measured at end-diastole and at end-systole following the recommendations for standardization.[7-8]

M-mode echocardiographic estimates of LV volume are known to be limited by several geometrical assumptions. For this reason we selected an ellipsoid biplane area-length model derived from two-dimensional left ventricular image (short-axis section at the mitral level and apical four-chamber view). This method is sufficiently accurate for clinical use and can be measured in most patients.[9]

Indices of Left Ventricular Performance

Fractional shortening (FS) and ejection fraction (EF) were used to estimate the overall pattern of LV systolic shortening. FS was derived from M-mode tracings as: EDD-ESD/EDD, where EDD and ESD are the LV dimensions at end-diastole and at end-systole. EF was derived from 2D-calculated volumes as: EDV-ESV/EDV, where EDV and ESV are the LV volumes at end-diastole and at end-systole.

We used both indices for several reasons: FS is often used to indicate the limit of a normal LV function in asymptomatic patients with AI;[10-13] therefore, it allows comparison with different series of patients. Moreover, its calculation is so easy to permit an immediate control of LV function modifications during each experimental condition. EF is a better index of LV pump function and was previously used to construct the LV pump performance-myocardial contractility relationship in patients with severe chronic aortic insufficiency.[14]

Left Ventricular Relative Wall Thickness

Radius to thickness ratio was determined from M-mode echocardiograms as: R/Th=(EDD/2)Th, where EDD is the dimension at end-diastole and Th is the wall thickness at end-diastole. This index is linearly related to the LV volume/mass ratio within a wide range of LV sizes and is independent on LV geometry.[11,15] This ratio reflects the degree to which LV hypertrophy is appropriate to match the afterload increase due to the chronic volume overload.

Wall Stress Index

Noninvasive indices of LV wall stress can be estimated when combining arterial systolic blood pressure measurements (cuff method) simultaneously with echocardiographic measurement of LV radius and the average of the septal and posterior wall thickness (R/Th_{mean}). Excellent correlations between echocardiographic determined values of mean LV meridional wall stress (MWS) and peak LV wall stress calculated from cineangiocardiograms have been reported.[16] Mean wall stress can be determined as: $PAP \cdot R/Th_{mean}$, where PAP is the peak systolic arterial pressure.

Assessment of Myocardial Contractility

It has been demonstrated[17] that the slope of the line connecting the upper left corners of LV pressure-volume loops

(E_{max}) can be used as an index of myocardial contractility. The determination of E_{max} requires repeated measurements of LV pressure and volume over a wide range of loading conditions. This is difficult to do in clinical setting. Some investigators have therefore used the peak systolic pressure–volume relationship as a practical alternative to estimate E_{max}.[18,19] This enables the peak systolic pressure to end-systolic volume (PAP/ESV) ratio to be evaluated noninvasively by measuring the peak systolic pressure by the cuff method and the end-systolic volume by two-dimensional echocardiography.[20] From a theoretical point of view, PAP/ESV which is derived from a single point on the pressure-volume loop, is not as reliable an index of myocardial contractility as the E_{max}. Despite this limitation, several studies have applied this index as a useful index of LV contractility in clinical setting.[11-13,21-24] Thus in this study we used PAP/ESV to estimate the LV myocardial contractility. Its clinical validity was also confirmed by a close agreement with the cineangiographic values.[14]

Statistical Analysis

Comparison between groups was made with analysis of variance, analysis of covariance, and *t*-test when appropriate. Linear regression analysis was employed to assess the relation between EF and MWS. Interpolation with a logarithmic curve was used to describe the relation between EF and PAP/ESV.

Results

The echocardiographic parameters of the study patients are listed in Table I.

Group A patients had normal FS and EF, an adequate hypertrophy (R/Th less than 4), normal or nearly normal values of the myocardial contractility index (PAP/ESV), and a moderate increase of MWS at control echocardiographic examination. These patients are distributed on the plateau of the LV pump function-myocardial contractility relationship (EF vs. PAP/ESV); this relation was previously described in patients with severe chronic aortic insufficiency.[14] In Group A patients, PAP/ESV was significantly higher ($p<.001$) and MWS was significantly lower ($p<.001$) than in Group B and Group C patients. The decrease of MWS after nifedipine was due to a reduction both on LV cavity dimensions and on peak arterial systolic pressure (492 ± 70 vs. 398 ± 50; $p<.01$); heart rate and myocardial contractility did not change significantly. Thus, their position on the pump function-myocardial contractility relation was unchanged after nifedipine. Their pump function–mean wall stress relation was instead displaced toward a more advantageous condition on LV load (Fig. 1).

Thirty-four patients had an abnormal FS and EF at control echocardiogram: 22 of these had normalization (Group B) and 12 patients maintained abnormal values of LV pump function indices after nifedipine. Control values of R/Th, FS, EF, LV cavity dimensions and volumes, and MWS were not significantly different between Group B and Group C patients; but Group C patients had a more depressed basal level of myocardial contractility ($3.1\pm.3$ vs. $1.9\pm.3$; $p<.001$). In both groups B and C, MWS decreased significantly after nifedipine without changes in PAP/ESV ratio; heart rate did not increase significantly. The pump function–MWS relation shows the advantageous unloading action of nifedipine on LV performance of Group B patients (Fig. 2): patients were displaced to a new relation with a normal pump function. Moreover,

TABLE I Echocardiographic data of study patients (mean values ± SD)

	Normal subjects	Group A (n=14)		Group B (n=22)		Group C (n=12)		
	(n=26)	B	N	B	N	B	N	N±D
EDD (mm)	48±3	68±4	64±4	70±6	66±4	72±8	70±6	70±6
ESD (mm)	33±4	46±6	40±8	50±4	44±4	52±6	51±4	48±4
FS (%)	38±4	36±4	34±4	26±2	35±2	25±2	26±3	30±4
EDV (ml/m²)	76±10	120±12	108±16	132±14	116±12	136±16	124±22	122±18
ESV (ml/m²)	14±4	38±14	23±10	62±16	44±10	66±12	62±18	50±14
EF (%)	78±6	70±8	78±6	54±6	66±6	50±4	55±5	60±4
R/Th	2.8±.4	3.2±.2		3.4±.3		3.4±.4		
MWS ($dyn \cdot cm^{-2} \cdot 10^3$)	248±42	492±70	398±50	615±92	508±70	676±123	524±114	548±98
PAP/ESV	4.5±.4	4±.4	3.9±.5	3.1±.3	3±.4	1.9±.3	1.9±.3	2.3±.5
HR (beats/min)	74±6	72±8	76±6	70±4	74±6	78±6	78±10	72±8

Abbreviations: EDD = end-diastolic dimension; ESD = end-systolic dimension; FS = fractional shortening; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; R/Th = radius/thickness ratio; MWS = mean wall stress; PAP/ESV = peak arterial pressure/end-systolic volume ratio; HR = heart rate; N = nifedipine; D = digoxin; B = baseline.

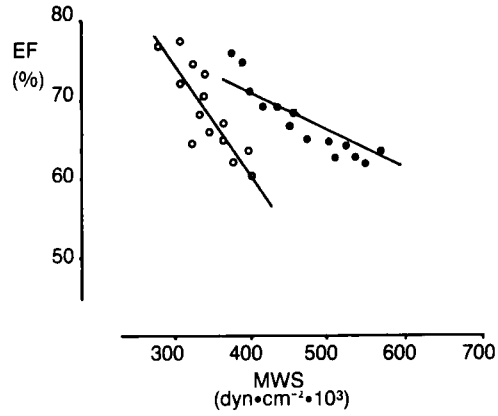

FIG. 1 Control and after nifedipine relations between left ventricular pump function (EF=ejection fraction) and afterload (MWS=mean wall stress) in Group A patients (n=14) with normal control values of ejection fraction. •, control: y=99−.88x; r=.92; p<.001; ○, nifedipine: y=120−.15x; r=.91; p<.001

nifedipine was not able to shift the Group C patients to a new pump function-MWS relation. These patients moved on the control relation with a mild to moderate increase on EF.

Both Group B and Group C patients had a new pump function-myocardial contractility relation after nifedipine, but only Group B patients with a control value of PAP/ESV greater than 2.5 reached the plateau of the relation with normal levels of LV pump function (Fig. 3).

The 12 Group C patients without normalization of pump function after nifedipine alone, were administered simultaneously 20 mg sublingual nifedipine and 0.5 mg intravenous digoxin. Only the 4 patients with a control value of PAP/ESV greater than 2 had normalization of pump function indices due to a significant increase on myocardial contractility and decrease on MWS (Fig. 4).

Discussion

It is well recognized that the chronically volume-overloaded left ventricle can develop irreversible structural and functional damage even if the patient remains asymptomatic. Such myocardial damage could preclude a successful aortic valve replacement. However, a premature valve replacement must be avoided because the ratio between benefits (mainly the long-term protection on myocardial function) and complications remains an unresolved problem in asymptomatic patients.[25]

Thus, the asymptomatic patients with severe chronic aortic insufficiency (AI) must be followed closely by serial noninvasive studies of left ventricular function in an attempt to prevent the development of irreversible left ven-

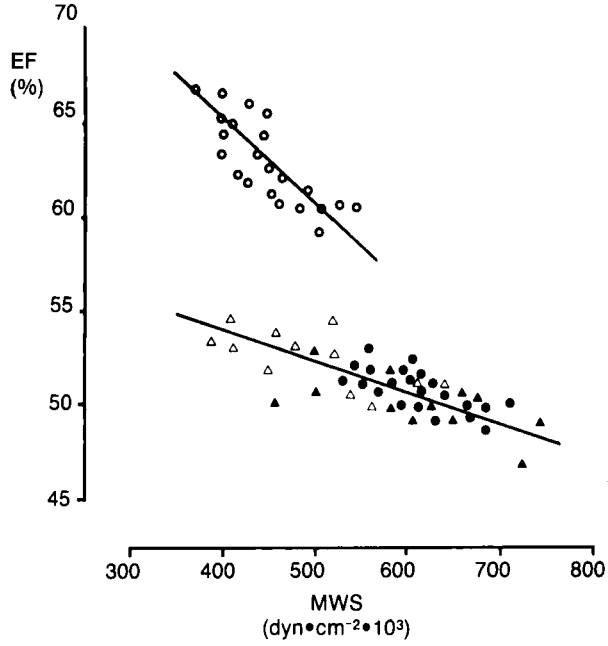

FIG. 2 Control (Group B, •; Group C, ▲) and after nifedipine (Group B, ○; Group C, △) left ventricular pump function-afterload relation in patients with control abnormal values of ejection fraction (EF=ejection fraction; MWS=mean wall stress). Group B: n=22; y=78−.04x; r=.71; p<.01; Group C: y=88−.02x; r=.88; p<.001

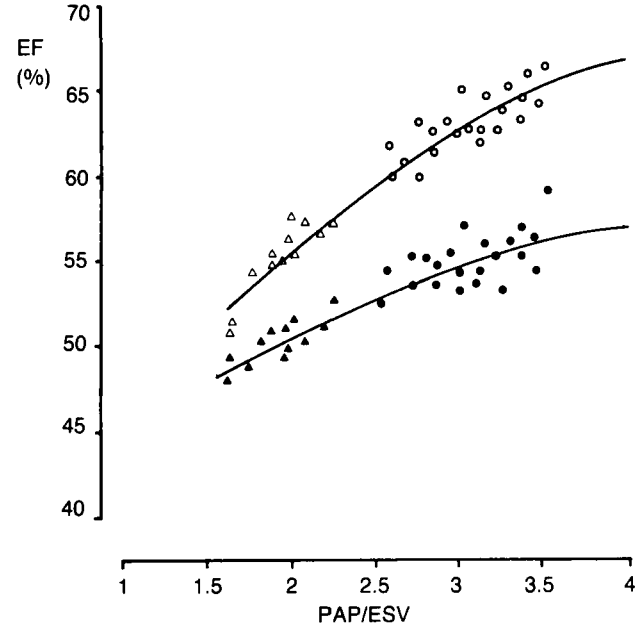

FIG. 3 Control (•, Group B; ▲, Group C) and after nifedipine (○, Group B; △, Group C) left ventricular pump function-myocardial contractility relations in Group B (n=22) and C (n=12) patients (EF=ejection fraction, PAP/ESV=peak arterial pressure-to-end-systolic volume ratio). Group B: y=43.6±18.4 lnx; r=.72; p<.001; Group C: y=45.8+8.3lnx; r=.86; p<.001

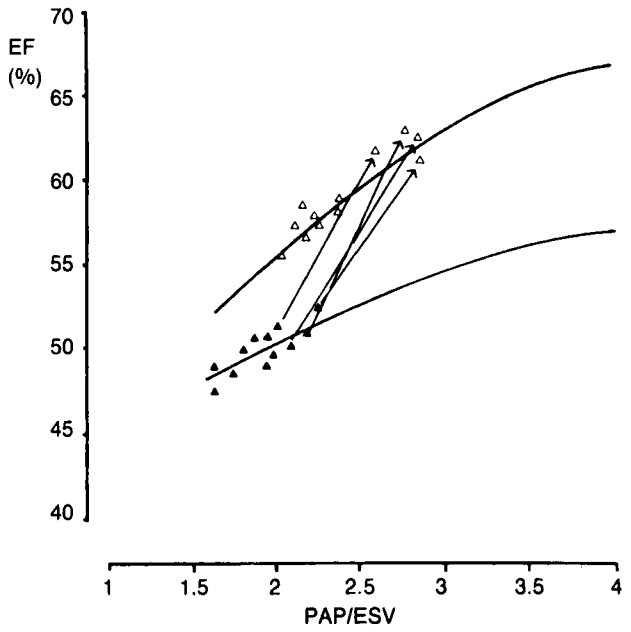

FIG. 4 Group C (n=12) patients relative position to left ventricular pump function-myocardial contractility relations reported in Figure 3, after combined administration of nifedipine and digoxin (△). (▲) Control.

tricular dysfunction. It has been demonstrated that echocardiographic measurements of left ventricular function have considerable predictive value.[11]

In order to define a rational pharmacological approach of asymptomatic patients with AI, it is important to know the causes determining the irreversible myocardial lesions (loss of cardiac cells, fibrosis and cavity dilatation with "plastic change").[1] The modifications in left ventricular loading conditions with an increased left ventricular wall stress and a decreased myocardial efficiency (defined as the ratio of external work to total energy consumed) are well known factors leading to irreversible damage.[2] The secondary hypertrophic process itself can lead to myocellular contractile dysfunction.[26]

Thus, the unloading agents increase myocardial efficiency by decreasing left ventricular wall stress; in addition, the reduced afterload allows more of the energy to be expended in ejecting blood rather than in developing pressure.[2] Finally, the reduced level of wall stress limits the stimulus to the secondary hypertrophy.

Recently, the underperfusion of subendocardium[3] and microvascular spasm[1] have been recognized as potential factors of irreversible myocardial lesions. Thus, among the vasodilators, special attention must be paid to the calcium-channel blockers such as nifedipine. This agent can decrease the left ventricular afterload, increase the coronary flow and the perfusion of the subendocardial muscle, and prevent phenomena of microvascular spasm.[4,5] The complex energy-sparing activity of nifedipine could maintain the ultrastructure of the cell surface, so it could avoid or delay the loss of cardiac cell function and the onset of necrosis.[27]

The concept of afterload mismatch[28] has been recognized as a reversible cause of impaired pump performance in patients with chronic aortic valve disease.[19,29,30] However, separating the effect of myocardial contractile dysfunction from that of afterload mismatch on pump performance is difficult in a clinical setting. None of the single indices of left ventricular performance can define such complex aspects of myocardial function.[31,32] The relationship between EF and MWS[18,30,33] and the left ventricular pump performance-myocardial contractility relationship (EF vs. PAP/ESV)[14,34] have been used to assess the pattern of left ventricular function in chronically overloaded ventricles.

In our study, patients with normal control pump function (EF, FS) had an important reduction on MWS after nifedipine. These patients moved to a new left ventricular pump function–afterload relationship (EF vs. MWS) (Fig. 1): a normal left ventricular pump function was maintained with a more advantageous loading condition. These patients are distributed on the plateau of the pump function-myocardial contractility relationship and their pattern of left ventricular performance is stable at least for 36 months.[13] Thus, it seems justified to test the maintenance of the favorable action of nifedipine on left ventricular function in a long-term clinical trial.

In patients with abnormal control levels of EF and FS, the nifedipine-induced reduction on left ventricular afterload normalized the systolic shortening only in patients with a basal value of PAP/ESV greater than 2.5. The role of afterload mismatch in determining a depressed left ventricular pump function in these patients was demonstrated by the shift to differing EF-MWS and EF-PAP/ESV relationships (Figs. 2 and 3): for any level of myocardial contractility, the left ventricular pump function increases after nifedipine, but the difference between the basal and post-nifedipine EF-PAP/ESV relation increases by increasing the basal level of myocardial contractility. Thus, in patients with a mild to moderate decrease of myocardial contractility, an excess on left ventricular wall stress determines a reduced level of control pump function, reversible by the unloading action of nifedipine (Fig. 2).

In patients without normalization of EF and FS after nifedipine, the depressed control left ventricular pump function is not entirely due to an afterload mismatch mechanism and the depressed myocardial contractility is a main determining factor. Thus, these patients had a combined unloading and positive inotropic intervention (nifedipine plus digoxin). The increase of PAP/ESV in response to digoxin is clearly related to the control level of myocardial contractility: the higher the control level of myocardial contractility the more important is its increase after digoxin, and only four patients with a control value of PAP/ESV greater than 2 had normalization of left ventricular pump function (Fig. 4).

A long-term follow-up study of the effect of protracted nifedipine therapy is justified in patients with normalization of left ventricular pump function indices after acute sublingual nifedipine administration. In fact, even when FS values of less than 29% were used as indications of aortic valve replacement in asymptomatic patients with severe aortic insufficiency[10] it was recently demonstrated that irreversible myocardial damage did not appear during follow-up of 36 months and the delayed aortic valve replacement had a good result.[13] Afterload excess is a significant cause of left ventricular performance deterioration, thus the possibility exists that early intervention with a potent unloading cardioprotective agent might prevent or delay myocardial deterioration. Moreover, prolonged observation of the ability of the left ventricle to respond favorably to valve replacement at a later time is also unknown.[25,35]

Aortic valve replacement is indicated in asymptomatic patients without normalization of left ventricular pump function after associated administration of nifedipine and digoxin. Pharmacological therapy as an alternative to aortic valve replacement, whose result is excellent in these patients, is not justified.[13,31]

More difficult is the task of choosing the correct approach of asymptomatic patients with normalization of left ventricular pump function after combined use of unloading and a positive inotropic agent. These patients have more advanced myocardial damage with respect to Group B patients and a multivariate analysis of long-term surgical and pharmacological effects on left ventricular function is necessary.

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