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Prognostic Importance of the Immediate Hemodynamic Response to Nifedipine in Patients With Severe Left Ventricular Dysfunction

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To determine the clinical significance of the occurrence of hemodynamic deterioration after the administration of calcium channel blocking drugs, nifedipine (20 mg orally) was administered to 29 patients with severe left ventricular dysfunction. Thirteen patients showed hemodynamic improvement with the drug (Group 1), as shown by a notable increase in cardiac index associated with a modest decrease in mean arterial pressure. The other 16 patients exhibited hemodynamic deterioration after nifedipine (Group 2), as reflected by a decline in right and left ventricular stroke work indexes accompanied by a marked hypotensive response. These differences were not related to differences in the peripheral vascular response to nifedipine, because both groups showed similar decreases in systemic and pulmonary vascular resistances.

Groups 1 (hemodynamic improvement) and 2 (hemodynamic deterioration) were similar with respect to all demographic variables and pretreatment left ventricular performance (cardiac index, left ventricular filling pressure and systemic vascular resistance). Yet, the 1 year actuarial survival in patients in Group 1 was substantially better than that in patients in Group 2 (67 versus 23%, $p = 0.009$). Group 2, however, had higher values for plasma renin activity (17.7 ± 6.0 versus 4.3 ± 1.4 mg/ml per h, $p < 0.05$), lower values for serum sodium concentration (134.6 ± 1.2 versus 139.2 ± 0.6 mEq/liter, $p < 0.05$) and higher values for mean right atrial pressure (15.8 ± 2.0 versus 7.9 ± 1.4 mm Hg, $p < 0.01$) than did patients in Group 1. Previous work has identified these three variables as important determinants of survival in patients with severe chronic heart failure; yet, the hemodynamic response to nifedipine was more powerful than any of these three variables in predicting long-term prognosis.

These findings confirm the hypothesis that patients with the most advanced heart failure (as reflected by their poor long-term survival) are most likely to show hemodynamic deterioration after calcium channel blockade, and they suggest that the assessment of neurohormonal activation and right ventricular performance more accurately identifies such patients than do conventional measures of left ventricular performance.

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Patients with severe chronic heart failure have a highly unfavorable long-term prognosis; 30 to 50% of patients with advanced left ventricular dysfunction who remain symptomatic on digitalis and diuretic therapy die within 1 year, and 60 to 80% die within 2 years (1–7). A variety of clinical, hemodynamic and hormonal variables have been identified that correlate with mortality in these patients, but the relative importance of these variables has varied according to the population under study. In studies (1,2) that evaluated patients with a wide range of symptoms, hemodynamic variables (such as cardiac index, left ventricular filling pressure and left ventricular stroke work index) were powerful prognostic variables. In contrast, in studies (4,6,7) that confined their evaluation to very ill patients, neurohormonal activation and right ventricular function were the principal predictors of long-term survival. Unfortunately, all of the variables evaluated in these previous studies were indirect reflections of the severity of the underlying degree of myocardial impairment, because direct measurements of myocardial contractile force are nearly impossible to perform in the clinical setting; conventional hemodynamic variables are

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highly load dependent (8), and sophisticated calculations of stress-shortening relations are difficult to interpret in patients with asymmetric left ventricular dysfunction and dilation (9).

Conceptually, an excellent approach to assessing the integrity of the intrinsic myocardial contractile apparatus is to measure the response of patients with left ventricular dysfunction to the administration of a negative inotropic agent. Insofar as patients with the greatest degree of myocardial impairment would be expected to show the most marked hemodynamic deterioration after pharmacologic cardiodepression, the administration of such an agent (for example, a calcium-entry blocker) could provide important prognostic information. Because calcium is essential for activation of contractile proteins, calcium channel blocking drugs exert potent direct negative inotropic effects in isolated cardiac muscle preparations (10,11). In patients with normal cardiovascular function, this cardiodepressant action is offset by the systemic vasodilator effects of these drugs; the resultant activation of the sympathetic nervous system and the reduction of ventricular afterload act to maintain ventricular performance (12–15). In patients with compromised left ventricular function, however, there is an impaired ability to deliver calcium ions to myofibrillar elements (16,17); hence, the myocardium is exquisitely sensitive to agents that further reduce the availability of intracellular calcium (18). In addition, the sympathetic nervous system is already greatly activated in these patients, and adrenergic reflex mechanisms that are crucial to the support of circulatory homeostasis during calcium channel blockade are markedly attenuated (19,20). Consequently, these patients may experience notable hemodynamic and clinical deterioration after the administration of calcium channel blocking drugs (21–27). Can such a pharmacologic response be used to predict long-term survival in these patients? The present analysis was designed to address this question.

Methods

Study patients. The study group consisted of 29 patients with chronic congestive heart failure, who received a trial of nifedipine for therapeutic purposes, on the basis of reports of hemodynamic and clinical improvement after short- and long-term therapy with the drug (28–31). All patients had a left ventricular ejection fraction <35% as determined by radionuclide ventriculography. There were 19 men and 10 women, aged 27 to 80 years (mean 61). The cause of heart failure was coronary artery disease in 15 patients, primary dilated cardiomyopathy in 13 and persistent severe left ventricular dysfunction after mitral valve replacement in one patient. All patients were evaluated while clinically stable.

Hemodynamic determinations. Before entry into the study, all patients were hospitalized for a minimum of 5 days, during which time doses of digitalis and diuretics remained constant and all vasodilator drugs were discontinued. After written, informed consent was obtained, right heart catheterization and arterial cannulation were performed for measurement of intracardiac and systemic pressures, respectively; patients were then permitted to rest overnight to permit dissipation of hemodynamic changes related to intravascular instrumentation (32). Left ventricular filling pressure was estimated by the mean pulmonary capillary wedge pressure. Thermodilution cardiac output was determined in triplicate by a bedside cardiac output computer using iced injectate. Patients were kept at bed rest and in a postprandial state during all hemodynamic measurements to avoid circulatory changes that accompany eating or changes in position.

Drug administration. The following hemodynamic variables were measured repeatedly for at least 2 hours (with a variation of <10%) to ensure stability of the pretreatment state before drug administration: mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure and cardiac output. Each patient then received a single dose of 20 mg of nifedipine orally. This dose was chosen because of its established utility in the treatment of ischemic heart disease and because similar doses of the drug have been evaluated in previous studies of patients with left ventricular dysfunction (22,30,31,33–37). After drug administration, all hemodynamic variables were reassessed every 15 minutes for 1 hour and then every 30 minutes for an additional 2 hours.

Biochemical determinations. Blood samples were collected before the administration of nifedipine for determination of serum sodium concentration, blood urea nitrogen and serum creatinine concentration in all patients and for measurement of plasma renin activity in 22 of the 29 patients. All samples were drawn at a similar time of the day, while patients were consuming a 2 g sodium diet, and after at least 4 hours in the supine position.

Long-term clinical follow-up. After completion of the invasive hemodynamic studies, all patients were treated with isosorbide dinitrate, hydralazine or captopril, alone or in combination, in addition to digitalis and diuretics; no patient received long-term treatment with any calcium channel blocking drug. In 25 of the 29 patients, long-term survival was assessed from the day of nifedipine administration to the day of death or, if alive, to the date of the present analysis; all patients were followed up for at least 1 year. Long-term follow-up data were not available in four patients.

Data analysis. Mean systemic and pulmonary artery pressures were determined by electronic filtration. Derived hemodynamic variables were calculated as follows:

Cardiac index (CI) = CO/body surface area (liters/min per m^2),

Stroke volume index (SVI) = CI/heart rate (ml/m^2),

LV stroke work index (LVSWI) =
(MAP − LVFP) × SVI × 0.0136 (g-m/m^2),

RV stroke work index (RVSWI) =
(MPAP − MRAP) × SVI × 0.0136 (g-m/m^2),

Systemic vascular resistance =
80 × (MAP − MRAP)/CO (dynes·s·cm^{-5}),

Pulmonary vascular resistance =
80 × (MPAP − LVFP)/CO (dynes·s·cm^{-5}),

where CO = cardiac output, MAP = mean systemic arterial pressure, LV = left ventricular, RV = right ventricular, LVFP = left ventricular filling pressure, MPAP = mean pulmonary artery pressure and MRAP = mean right atrial pressure.

The hemodynamic effects of nifedipine were assessed at the peak effect of the drug on systemic vascular resistance, 30 to 60 minutes after its administration. Patients were then classified into two groups based on whether the change in left ventricular stroke work index after the administration of nifedipine was greater than or less than the mean decline of 25%; this variable was used because it reflects global left ventricular performance better than do the other hemodynamic variables we measured and has been used to distinguish among subgroups treated with vasodilator drugs in previous studies (38,39). In 16 patients, nifedipine produced a ≥25% decline in left ventricular stroke work index; these patients were considered to have had hemodynamic deterioration during the study (Group 2). In the remaining 13 patients, nifedipine produced little change (≤15%) or an increase in left ventricular stroke work index; these patients showed marked increases in cardiac output and were considered to have had hemodynamic improvement (Group 1). Quantitative and qualitative differences between the two groups were evaluated by the *t* test for independent variables and by Fisher's exact test, respectively. The hemodynamic effects of nifedipine within each group were compared with their respective control values by the *t* test for paired data and with each other by analysis of variance. Cumulative survival curves were constructed using the Kaplan-Meier survivorship method (40), and differences between survival curves were tested for significance by both Mantel-Cox log-rank and Wilcoxon-Breslow methods (41,42). All group data are expressed as mean ± SEM.

Results

In the 29 patients in our study, nifedipine produced notable increases in cardiac index and stroke volume index and decreases in mean arterial pressure, left ventricular stroke work index and systemic and pulmonary vascular resistances without significant changes in left ventricular filling pressure or heart rate (Table 1).

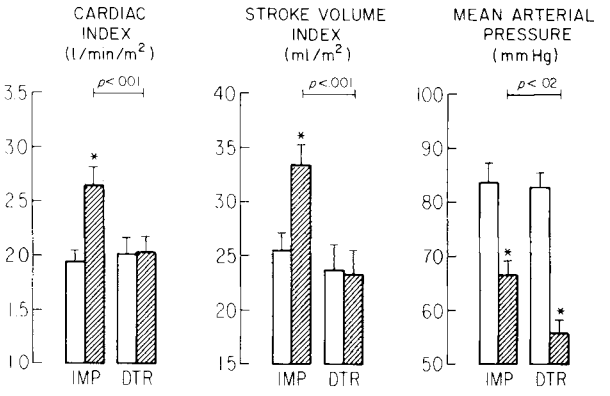
Differential hemodynamic effects of nifedipine in Groups 1 and 2 (Fig. 1 to 3). In the 13 patients in the hemodynamic improvement group (Group 1), nifedipine produced a marked increase in cardiac and stroke volume indexes (both $p < 0.001$) and a marked decrease in systemic and pulmonary vascular resistances (43 and 30%, respectively). These benefits were associated with moderate decrease in mean systemic arterial pressure (−17.2 mm Hg), but no significant change in right or left ventricular filling pressures, right or left ventricular stroke work indexes or

Table 1. Overall Hemodynamic Response to Nifedipine in All 29 Patients With Severe Chronic Heart Failure

	Control	Nifedipine	p Value*
Cardiac index (liters/min per m^2)	1.98 ± 0.09	2.31 ± 0.13	<0.01
Stroke volume index (ml/m^2)	24.5 ± 1.5	27.8 ± 1.7	<0.02
Left ventricular filling pressure (mm Hg)	24.9 ± 1.7	23.9 ± 1.4	NS
Mean arterial pressure (mm Hg)	83.2 ± 2.2	60.7 ± 2.0	<0.001
Mean right atrial pressure (mm Hg)	12.3 ± 1.4	13.4 ± 1.5	NS
Left ventricular stroke work index (g-m/m^2)	19.5 ± 1.4	14.8 ± 1.7	<0.001
Right ventricular stroke work index (g-m/m^2)	8.7 ± 0.7	7.8 ± 0.8	NS
Heart rate (beats/min)	81.8 ± 2.1	83.8 ± 3.3	NS
Systemic vascular resistance (dynes·s·cm^{-5})	1,851 ± 124	993 ± 70	<0.001
Pulmonary vascular resistance (dynes·s·cm^{-5})	346 ± 33	237 ± 24	<0.001

*Significance of differences between pretreatment and post-treatment values.

Figure 1. Values for cardiac index, stroke volume index and mean arterial pressure before and after nifedipine in patients with severe chronic heart failure who showed hemodynamic improvement (IMP) (Group 1) or hemodynamic deterioration (DTR) (Group 2) after administration of the drug. *$p < 0.001$, significance of difference between pre- and post-treatment values *within* each group; the p values at the **top of each panel** designate the significance of difference *between* the two groups in the magnitude of drug-induced changes. Group data are expressed as mean values ± SEM.



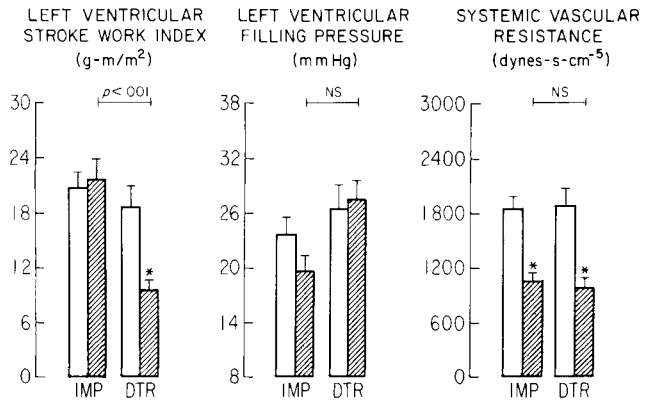
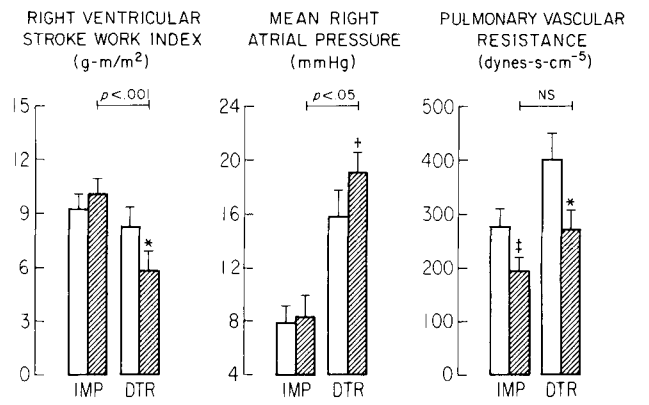


Figure 2. Values for left ventricular stroke work index, left ventricular filling pressure and systemic vascular resistance before and after the administration of nifedipine in Group 1 (IMP) and Group 2 (DTR). Format and abbreviations as in Figure 1. *p < 0.001.

heart rate. In contrast, despite decreases in systemic and pulmonary vascular resistances similar to those seen in Group 1 (49 and 32%, respectively), the 16 patients in the hemodynamic deterioration group (Group 2) showed a significant decline in right and left ventricular stroke work indexes (both $p < 0.001$) without an improvement in cardiac or stroke volume indexes. This unfavorable response was accompanied by a marked decrease in mean systemic arterial pressure (-27.0 mm Hg, $p < 0.001$), no change in left ventricular filling pressure and a significant increase in mean right atrial pressure ($+3.3$ mm Hg, $p < 0.01$). Of the hemodynamic variables measured in this study, the effects of nifedipine on cardiac and stroke volume indexes ($p < 0.001$), right and left ventricular stroke work indexes ($p < 0.001$), mean right atrial pressure ($p < 0.05$) and mean arterial pressure ($p < 0.02$) were significantly different between the two groups.

Figure 3. Values for right ventricular stroke work index, mean right atrial pressure and pulmonary vascular resistance before and after the administration of nifedipine in Group 1 (IMP) and Group 2 (DTR). Format and abbreviations as in Figure 1. *p < 0.001; †p < 0.01; ‡p < 0.05.



Pretreatment clinical and hemodynamic characteristics of Groups 1 and 2 (Table 2). Groups 1 and 2 were similar with respect to age, sex, etiology of heart failure, renal function, left ventricular ejection fraction and pretreatment values for cardiac and stroke volume indexes, left ventricular filling pressure, mean arterial pressure, right and left ventricular stroke work indexes, heart rate and systemic and pulmonary vascular resistances. Patients in Group 2, however, had significantly higher pretreatment values for mean right atrial pressure than did patients in Group 1 (15.8 ± 2.0 versus 7.9 ± 1.4 mm Hg, $p < 0.01$). The proportion of patients with a mean right atrial pressure ≥ 12 mm Hg was significantly greater in Group 2 (11 of 16 patients) than in Group 1 (2 of 13 patients), ($p < 0.02$). In addition, patients in Group 2 had higher pretreatment values for plasma renin activity (17.7 ± 6.0 versus 4.3 ± 1.4, $p < 0.01$) and lower pretreatment values for serum sodium concentration (134.6 ± 1.1 versus 139.2 ± 0.6, $p < 0.01$) than did patients in Group 1. The proportion of patients with a serum sodium concentration ≤ 137 mEq/liter was significantly greater in Group 2 (12 of 16 patients) than in Group 1 (2 of 13 patients) ($p < 0.02$).

Differential clinical effects of nifedipine in Groups 1 and 2. Eight (28%) of the 29 patients in this study experienced dyspnea or dizziness, or both, within 60 minutes after the administration of nifedipine. In three patients, these adverse reactions were mild and disappeared without specific therapy as the hemodynamic effects of the drug waned over time. Five patients, however, developed a clinical picture of cardiogenic shock (severe dyspnea and profound symptomatic hypotension) that was not responsive to intravenous calcium chloride and required intravenous levarterenol for blood pressure support for 4 to 10 hours after the administration of nifedipine. All patients recovered uneventfully, and repeat hemodynamic evaluation performed 24 hours later showed a return of all hemodynamic variables to pre-nifedipine values. Values for serum sodium concentration and plasma renin activity in these five patients varied from 126 to 135 mEq/liter and from 3.1 to 64.0 ng/ml per h, respectively. Of the seven patients in our study with a pretreatment plasma renin activity >10 ng/ml per h, three experienced cardiovascular collapse after administration of the drug and required intravenous pressors for blood pressure support. In contrast, only one of nine patients with a plasma renin activity <3 ng/ml per h experienced any adverse clinical effects, and this reaction consisted of transient dyspnea that did not require specific therapy.

Long-term follow-up. After completion of the nifedipine study, all patients were treated with isosorbide dinitrate, hydralazine or captopril, alone or in combination, and followed up for at least 1 year. The treatment regimens used and the duration of follow-up were similar in the two groups (762 ± 114 days in Group 1 and 643 ± 80 days in Group

Table 2. Pretreatment Clinical, Biochemical and Hemodynamic Variables in Patients in Groups 1 and 2

	Group 1 (n = 13)	Group 2 (n = 16)	p Value*
Age	66.1 ± 3.4	56.8 ± 4.0	NS
Sex	8M, 5F	11M, 5F	NS
Cause of CHF	ICM 8, PDC 5	ICM 7, PDC 8, MVR 1	NS
LV ejection fraction	0.20 ± 0.02	0.17 ± .01	NS
Serum sodium (mEq/liter)	139.2 ± 0.6	134.6 ± 1.1	<0.01
BUN (mg/dl)	39.6 ± 7.0	50.9 ± 6.4	NS
Serum Cr (mg/dl)	1.5 ± 0.1	1.6 ± 0.2	NS
PRA (ng/ml per h)	4.3 ± 1.4	17.7 ± 6.0	<0.01
CI (liters/min per m^2)	1.95 ± .11	2.01 ± .15	NS
SVI (ml/m^2)	25.4 ± 1.7	23.7 ± 2.4	NS
HR (beats/min)	77.8 ± 2.9	85.0 ± 2.8	NS
LVFP (mm Hg)	23.2 ± 1.9	26.3 ± 2.6	NS
MAP (mm Hg)	83.7 ± 3.7	82.9 ± 2.6	NS
MRAP (mm Hg)	7.9 ± 1.4	15.8 ± 2.0	<0.01
LVSWI ($g\text{-}m/m^2$)	20.8 ± 1.7	18.5 ± 2.2	NS
RVSWI ($g\text{-}m/m^2$)	9.2 ± 0.8	8.2 ± 1.1	NS
SVR ($dynes\cdot s\cdot cm^{-5}$)	1,824 ± 143	1,874 ± 197	NS
PVR ($dynes\cdot s\cdot cm^{-5}$)	278 ± 36	401 ± 50	NS

*Significance of differences between the two groups. BUN = blood urea nitrogen; CHF = congestive heart failure; CI = cardiac index; Cr = creatinine; F = female; HR = heart rate; ICM = ischemic heart disease; LV = left ventricular; LVFP = left ventricular filling pressure; LVSWI = left ventricular stroke work index; M = male; MAP = mean arterial pressure; MRAP = mean right atrial pressure; MVR = mitral valve replacement for valvular heart disease; PDC = primary dilated cardiomyopathy; PRA = plasma renin activity; PVR = pulmonary vascular resistance; RVSWI = right ventricular stroke work index; SVI = stroke volume index; SVR = systemic vascular resistance.

2). In Group 1, patients were treated with a converting enzyme inhibitor alone (four patients), a direct-acting vasodilator alone (four patients) and both classes of drugs in combination (five patients). In Group 2, patients were treated with a converting enzyme inhibitor alone (six patients), a direct-acting vasodilator alone (six patients) and both classes of drugs in combination (four patients).

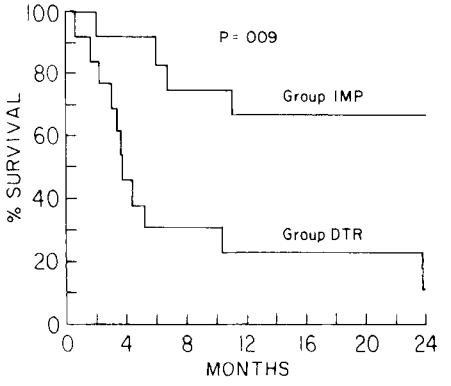
During the course of follow-up, patients in Group 1 fared significantly better than did patients in Group 2 (median survival 486 versus 108 days, respectively; $p = 0.009$ by Mantel-Cox and Wilcoxon-Breslow) (Fig. 4); the 1 year actuarial survival was 67% in Group 1 compared with 23% in Group 2. At the time of most recent follow-up, the proportion of patients who were alive was significantly greater in Group 1 (8 of 12 patients) than in Group 2 (2 of 13 patients) (67 versus 15%, $p < 0.05$).

All pretreatment clinical, hemodynamic and biochemical variables shown in Table 2 (except for plasma renin activity) were entered together with the observed hemodynamic response to nifedipine into a Cox proportional hazards model with the use of stepwise regression analysis; because plasma renin activity was measured in only 22 patients, it was not entered into this analysis. Of all variables that were significantly different between Groups 1 and 2, the change in left ventricular stroke work index after nifedipine was the most powerful predictor of long-term survival.

Discussion

The findings of the present study confirm previous observations that nifedipine may cause hemodynamic improvement or deterioration in patients with congestive heart failure (22). Nearly half of our patients (Group 1) showed

Figure 4. Kaplan-Meier analysis showing cumulative rates of survival in patients who had severe chronic heart failure stratified into two groups on the basis of their immediate hemodynamic response to a single dose of nifedipine (Groups 1 [IMP] and 2 [DTR]) but who received long-term treatment with conventional vasodilator drugs (nitrates, hydralazine and captopril). Patients who had hemodynamic improvement after nifedipine (Group 1) fared significantly better than did patients who had hemodynamic deterioration (Group 2) ($p = 0.009$, Wilcoxon-Breslow and Mantel-Cox).



notable hemodynamic improvement after nifedipine, as manifested by a marked increase in cardiac index that was accompanied by only a modest decline in mean arterial pressure. In contrast, the other half of our patient cohort (Group 2) experienced notable hemodynamic deterioration after nifedipine, as reflected by a decline in right and left ventricular stroke work indexes that was accompanied by a marked hypotensive response. These differences could not be explained by differences in the peripheral vascular response to nifedipine (22), because both groups showed similar decreases in systemic and pulmonary vascular resistance. They also could not be ascribed to changes in loading conditions, because (in addition to similar changes in systemic vascular resistance) right and left ventricular filling pressures failed to change significantly in either group. Hence, we must attribute the different hemodynamic responses we observed in the two groups to a significant depression of myocardial contractility induced by nifedipine in Group 2.

Nifedipine response as a measure of disease severity. Why should patients in the hemodynamic deterioration group have been so exquisitely sensitive to the cardiodepressant effects of nifedipine? The delivery of calcium to the contractile proteins is thought to be profoundly compromised in states of severe myocardial dysfunction (16,17) and, thus, any drug that impedes the movement of calcium into the cell can critically impair contractile performance (43). Consequently, we should be able to assess the integrity of the intrinsic myocardial contractile apparatus by measuring the response of patients with left ventricular dysfunction to the administration of a negative inotropic agent. Recent experience with beta-adrenergic blocking drugs suggests the validity of this approach. Patients with heart failure who have the highest circulating levels of norepinephrine (44) and the most severe histologic changes on myocardial biopsy (45) are most susceptible to hemodynamic deterioration after short-term beta-receptor blockade; such hormonal or histologic markers also identify patients with heart failure who have the most unfavorable long-term prognosis (6,46). No previous study, however, has shown a direct relation between the short-term hemodynamic response to a cardiodepressant drug and long-term survival. Our observation that the response to nifedipine was the most powerful predictor of long-term prognosis 1) strongly supports the concept that patients with the most advanced heart failure (as determined by their high mortality) have the greatest susceptibility to the administration of a negative inotropic agent; and 2) suggests that the availability of calcium to myofibrillar elements declines in parallel with the severity of the heart failure state.

Hemodynamic variables as a measure of disease severity. Because the response to nifedipine may be deleterious in patients with severe congestive heart failure, we would like to be able to measure the severity of the underlying disease process without the use of a "nifedipine challenge." Can conventional measures of left ventricular function identify the most severely ill individuals? In our study, as well as in previous reports (22), pretreatment values for cardiac output, left ventricular stroke work index, left ventricular filling pressure, systemic vascular resistance and left ventricular ejection fraction did not differ between the hemodynamic improvement and deterioration groups, and, thus, did not determine the susceptibility to adverse reactions after calcium channel blockade. Why do such conventional measures of cardiac performance fail to accurately assess the severity of myocardial impairment in patients with severe congestive heart failure? Conventional measures of ventricular function are load dependent (8,9) and, thus, do not accurately assess contractile function or the severity of the intrinsic disease process. Furthermore, clinically important changes in ventricular performance may be very difficult to discern in a patient whose myocardial function is already severely compromised. These concepts may explain why conventional hemodynamic variables (when severely abnormal) do not provide independent prognostic information in patients with severe heart failure (6,7), and why left ventricular function may show little deterioration during the long-term follow-up of these patients, even though the underlying disease presumably continues to progress and ultimately leads to the death of the patient (47).

Prognostic variables as a measure of disease severity. How then can we measure the severity of the underlying disease process and thereby identify those patients with heart failure whose contractile function is most dependent on available stores of intracellular calcium? Insofar as the severity of the disease process is the principal determinant of the survival of the myocardial cell, it would appear that variables that predict long-term survival would provide the most accurate estimate of disease severity and would therefore predict the susceptibility to calcium channel blockade. Accordingly, patients who experienced hemodynamic and clinical deterioration after treatment with nifedipine showed higher pretreatment values for plasma renin activity and mean right atrial pressure and lower pretreatment values for serum sodium concentration than did patients who tolerated the drug without difficulty; all three variables have been shown to be powerful predictors of long-term survival of patients with severe congestive heart failure (4,6,7,48). This observation may explain the findings of previous reports, in which nifedipine produced short-term hemodynamic improvement in most patients with heart failure (who generally have a normal serum sodium concentration and preserved right ventricular function) (49), but caused detrimental circulatory effects in patients who had markedly increased values for plasma renin activity or mean right atrial pressure before therapy (23,26). Yet, of all the predictive variables that we evaluated in the present study, the immediate hemodynamic response to nifedipine provided the most powerful prognostic information.

Alternative explanations for our observations should be considered. The elevated values for mean right atrial pressure in patients in the hemodynamic improvement group might reflect a marked expansion of intravascular volume, presumably the result of the notable activation of the renin-angiotensin system that we measured in these individuals. Such sodium retention could conceivably attenuate the responsiveness of peripheral vessels to vasodilator stimuli (50), and if the vasodilating effects of nifedipine were attenuated, the cardiodepressant effects of this drug might become more apparent (43). Although attractive, this sequence of events appears unlikely, however, because patients in the hemodynamic improvement and deterioration showed similar decreases in systemic vascular resistance. On the other hand, the adverse reactions that we noted in the hemodynamic deterioration group might have been the result of excessive vasodilation, resulting in a marked hypotensive response that may have compromised perfusion of the right and left ventricles. If true, the deterioration of right and left ventricular performance that we noted after nifedipine would not be the consequence of a direct negative inotropic action but would result from right and left ventricular ischemia, especially in patients who had severe obstructive coronary artery disease and who would have been highly susceptible to changes in coronary perfusion pressure. We do not believe, however, that the hypotensive effects of nifedipine in our patients were of primary pathophysiologic importance, because five hyponatremic patients in the hemodynamic deterioration group were subsequently treated with captopril and showed notable *increases* in cardiac output despite marked hypotensive responses (51) that were similar in magnitude to those seen after nifedipine. Therefore, the marked hypotensive response was likely the result (and not the cause) of the drug's cardiodepressant actions.

Limitations of the present study. Our study was designed only to evaluate the immediate hemodynamic tolerability of calcium channel blockade in patients with severe heart failure, and it did not attempt to assess the long-term utility or safety of this therapeutic approach in favorably altering loading conditions in the failing left ventricle. Although single doses of nifedipine produced short-term hemodynamic improvement in some patients (our hemodynamic improvement group), we do not wish to suggest that these favorable effects are necessarily sustained during long-term treatment or are accompanied by clinical benefits. There is little relation between the first-dose response to a vasodilator drug and the drug's long-term efficacy, whether patients are treated with conventional agents (52–54) or the calcium channel blocking drugs (37). Furthermore, doses of nifedipine that are well tolerated initially may produce cumulative deleterious effects during prolonged treatment. Our short-term data are important, however, in that they enable us to identify patients with severe heart failure who are so ill that they show *immediate* hemodynamic deterioration after an intervention that impedes the delivery of calcium ions to myofibrillar contractile elements. This risk is sufficiently great that we would advise strongly against the use of a "nifedipine challenge" (in clinical practice) to assess the severity of the underlying disease in patients with heart failure.

Conclusions. In conclusion, conventional measures of left ventricular function are an insensitive means of identifying patients with heart failure whose contractility is so severely impaired that cardiac performance deteriorates after calcium-entry blockade, despite drug-induced vasodilation. Although the measurement of conventional hemodynamic variables is valuable in the management of *acute* heart failure, clinically important changes in cardiac performance may be extremely difficult to discern in the patient whose myocardial function is severely and *chronically* impaired (55). Under such circumstances, the only sign of disease progression may be the onset of compromised end-organ perfusion, as reflected by the activation of endogenous neurohormones and the development of the hyponatremic state (7,56). Alternatively, patients with such severe impairment of myocardial contractility may be identified by determining their susceptibility to the administration of a cardiodepressant agent. Previous studies (6,7) have shown the prognostic importance of neurohormonal activation; the present study documents the prognostic significance of drug-induced cardiodepression. Therefore, in patients with severe chronic heart failure, central hemodynamic measurements at rest may provide little prognostic information unless the myocardium is pharmacologically stressed and should be considered less important than the adequacy of peripheral end-organ perfusion in assessing the severity of the underlying disease.

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References

1. Massie B, Ports T, Chatterjee K, et al. Long-term vasodilator therapy for heart failure: clinical response and its relationship to hemodynamic measurements. Circulation 1981;63:269–78.
2. Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1983;51: 831–6.
3. Wilson JR, Schwartz JS, St. John Sutton M, et al. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. J Am Coll Cardiol 1983;2:403–10.
4. Creager MA, Faxon DP, Halperin JL, et al. Determinants of clinical response and survival in patients with congestive heart failure treated with captopril. Am Heart J 1982;104:1147–54.
5. Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. Am J Cardiol 1984;54:147–52.

6. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.
7. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986;73:257–67.
8. Lang RM, Borow KM, Neumann A, Janzen D. Systemic vascular resistance: an unreliable index of left ventricular afterload. Circulation 1986;74:1114–23.
9. Borow KM, Green LH, Grossman W, Braunwald E. Left ventricular end-systolic stress-shortening and stress-length relationships in humans: normal values and sensitivity to inotropic states. Am J Cardiol 1982;50:1301–8.
10. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. Am J Cardiol 1980;46:1047–58.
11. Millard RW, Lathrop DA, Grupp G, Ashraf M, Grupp IL, Schwartz A. Differential cardiovascular effects of calcium channel blocking agents: potential mechanisms. Am J Cardiol 1982;49:499–506.
12. Ellrodt G, Chew CYC, Singh BN. Therapeutic implications of slow-channel blockade in cardiocirculatory disorders. Circulation 1980;62: 669–79.
13. Klein HO, Ninio R, Oren V, et al. The acute hemodynamic effects of intravenous verapamil in coronary artery disease: assessment by equilibrium-gated radionuclide ventriculography. Circulation 1983;67: 101–10.
14. Packer M, Leon M, Bonow RO, Kieval J, Rosing DR, Subramanian VB. Hemodynamic and clinical effects of combined verapamil and propranolol therapy in angina pectoris. Am J Cardiol 1982;50:903–12.
15. Packer M, Meller J, Medina N, et al. Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. Circulation 1982;65:660–8.
16. Harigaya S, Schwartz A. Rate of calcium binding and uptake in normal animal and failing human cardiac muscle: membrane vesicles (relaxing system) and mitochondria. Circ Res 1969;25:781–94.
17. Suko J, Vogel JHK, Chidsey CA. Intracellular calcium and myocardial contractility. III. Reduced calcium uptake and ATPase of the sarcoplasmic reticulum fraction from chronically failing calf hearts. Circ Res 1970;27:235–47.
18. Porter CB, Walsh RA, Badke FR, O'Rourke RA. Differential effects of diltiazem and nitroprusside on left ventricular function in experimental chronic volume overload. Circulation 1983;68:685–92.
19. Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. Am J Med 1965;39:442–51.
20. Chidsey CA, Sonnenblick EH, Morrow AG, Braunwald E. Norepinephrine stores and contractile force of papillary muscle from the failing human heart. Circulation 1966;33:43–51.
21. Chew CYC, Hecht HS, Collett JT, McAllister RG, Singh BN. Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. Am J Cardiol 1981;47:917–22.
22. Elkayam U, Weber L, McKay C, Rahimtoola S. Spectrum of acute hemodynamic effects of nifedipine in severe congestive heart failure. Am J Cardiol 1985;56:560–8.
23. Brooks N, Cattell M, Pidgeon J, Balcon R. Unpredictable response to nifedipine in severe cardiac failure. Br Med J 1980;281:1324.
24. Gillmer D, Karrk P. Pulmonary oedema precipitated by nifedipine. Br Med J 1980;280:1420–1.
25. Alves LE, Rose EP. Use of nifedipine in older patients and patients with congestive heart failure. Am J Med 1982;72:462.
26. Lefkowitz CA, Moe GW, Armstrong PW. Sublingual nitroglycerin and nifedipine in severe heart failure: a comparative evaluation (abstr). Circulation 1984;70(suppl II):II-114.
27. Gertz MA, Falk RH, Skinner M, Cohen AS, Kyle RA. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. Am J Cardiol 1985;55:1645.
28. Shen WF, Roubin GS, Hirasawa K, et al. Noninvasive assessment of acute effects of nifedipine on rest and exercise hemodynamics and cardiac function in patients with aortic regurgitation. J Am Coll Cardiol 1984;4:902–7.
29. Fioretti P, Benussi B, Scardi S, Klugmann S, Brower RW, Camerini F. Afterload reduction with nifedipine in aortic insufficiency. Am J Cardiol 1982;49:1728–32.
30. Klugmann S, Salvi A, Camerini F. Haemodynamic effects of nifedipine in heart failure. Br Heart J 1980;43:440–6.
31. Ludbrook PA, Tiefenbrunn AJ, Sobel BE. Acute hemodynamic responses to sublingual nifedipine: dependence on left ventricular function. Circulation 1982;65:489–98.
32. Packer M, Medina N, Yushak M. Hemodynamic changes mimicking a vasodilator drug response in the absence of drug therapy after right heart catheterization in patients with chronic heart failure. Circulation 1985;71:761–6.
33. Debaisieux J-C, Theroux P, Waters DD, Mizgala HF. Hemodynamic effects of a single oral dose of nifedipine following acute myocardial infarction. Chest 1980;78:574–9.
34. Fifer MA, Colucci WS, Lorell BH, Jaski BE, Barry WH. Inotropic, vascular and neuroendocrine effects of nifedipine in heart failure: comparison with nitroprusside. J Am Coll Cardiol 1985;5:731–7.
35. Leier CV, Patrick TJ, Hermiller J, et al. Nifedipine in congestive heart failure: effects on resting and exercise hemodynamics and regional blood flow. Am Heart J 1984;108:1461–8.
36. Bellocci F, Ansalone G, Santarelli P, et al. Oral nifedipine in the long-term management of severe chronic heart failure. J Cardiovasc Pharmacol 1982;4:847–55.
37. Agostoni PG, de Cesare N, Doria E, Polese A, Tamborini G, Guazzi MD. Afterload reduction: a comparison of captopril and nifedipine in dilated cardiomyopathy. Br Heart J 1986;55:391–9.
38. Packer M, Meller J, Medina N, Gorlin R, Herman MV. Importance of left ventricular chamber size in determining the response to hydralazine in severe chronic heart failure. N Engl J Med 1980;303: 250–5.
39. Chatterjee K, Parmley WW, Ganz W, et al. Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. Circulation 1973;48:1183–93.
40. Kaplan EL, Meier PL. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
41. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163–70.
42. Breslow NE. Covariance analysis of censored survival data. Biometrics 1979;30:89–99.
43. Josephson MA, Singh BN. Use of calcium antagonists in ventricular dysfunction. Am J Cardiol 1985;55:81B–8B.
44. Brinkley PF, Lewe RF, Lima JJ, Al-Awwa A, Unverferth DV, Leier CV. Hemodynamic-inotropic response to β-blocker with intrinsic sympathomimetic activity in patients with congestive cardiomyopathy. Circulation 1986;74:1390–8.
45. Valantine HA, Billingham ME, Heilbrunn SM, et al. Response to beta-blockers in dilated cardiomyopathy predicted by myocardial biopsy (abstr). Circulation 1986;74(suppl II):II-309.
46. Hammond EH, Anderson JL, Menlove RL. Prognostic significance of myofilament loss in patients with idiopathic cardiomyopathy determined by electron microscopy (abstr). J Am Coll Cardiol 1986;7: 204A.
47. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy in mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–53.

48. Lee WH, Packer M. Importance of right ventricular function as the primary determinant of clinical response and long-term survival in patients with severe heart failure treated with converting-enzyme inhibitors (abstr). J Am Coll Cardiol 1985;5:461.

49. Colucci WS, Fifer MA, Lorell BH, Wynne J. Calcium channel blockers in congestive heart failure: theoretic considerations and clinical experience. Am J Med 1985;78(suppl 2B):9–17.

50. Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. J Clin Invest 1968;47: 960–70.

51. Packer M, Medina N, Yushak M. Relation between serum sodium concentration and the hemodynamic and clinical responses to converting-enzyme inhibition with captopril in severe heart failure. J Am Coll Cardiol 1984;3:1035–43.

52. Packer M, Medina N, Yushak M, Meller J. Hemodynamic patterns of response during long-term captopril therapy for severe chronic heart failure. Circulation 1983;68:803–12.

53. Massie BM, Kramer BL, Topic N. Lack of relationship between short-term hemodynamic effects of captopril and subsequent clinical responses. Circulation 1984;69:1135–41.

54. Franciosa JA, Dunkman B, Leddy CL. Hemodynamic effects of vasodilators and long-term response in heart failure. J Am Coll Cardiol 1984;3:1521–30.

55. Firth BG, Dehmer GJ, Markham RV, Willerson JT, Hillis LD. Assessment of vasodilator therapy in patients with severe congestive heart failure: limitations of measurements of left ventricular ejection fraction and volumes. Am J Cardiol 1982;50:954–9.

56. Lilly LS, Dzau VJ, Williams GH, Rydstedt L, Hollenberg NK. Hyponatremia in congestive heart failure: implications for neurohormonal activation and response to orthostasis. J Clin Endocrinol Metab 1984;59: 924–30.