Diastolic function in patients with severe heart failure: comparison of the effects of enoximone and nitroprusside

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ABSTRACT To assess whether the phosphodiesterase inhibitor enoximone has a specific, direct effect on left ventricular diastolic function distinct from its inotropic and vasodilator actions, we compared the effects of enoximone and the pure vasodilator nitroprusside in 11 patients with severe heart failure. Mean (± SEM) left ventricular ejection fraction was 0.20 ± 0.03. Simultaneous left ventricular pressure and radionuclide angiographic volume were obtained at baseline, during infusion of nitroprusside, and after intravenous administration of enoximone. Left ventricular end-diastolic pressure (LVEDP) and volume (LVEDV) decreased with both agents (p < .01 vs control); LVEDP was lower for nitroprusside than for enoximone (p < .01) despite a similar LVEDV. Nitroprusside decreased the time constant of exponential left ventricular pressure decay, T_l (measured by the logarithmic method), from 84 ± 10 to 65 ± 8 msec (p < .01) but had no significant effect on T_D (measured by the derivative method), maximum negative dP/dt, or the peak rate of early diastolic filling. Enoximone shortened T_l from 86 ± 12 to 61 ± 9 msec (p < .01) and increased maximum negative dP/dt from 897 ± 101 to 1135 ± 134 mm Hg/sec (p < .01) but did not affect T_D or the peak filling rate. The left ventricular diastolic pressure-volume relation was shifted downward in only three of 11 patients on nitroprusside and three of 11 patients on enoximone, and these shifts were attenuated by adjusting for simultaneous changes in right atrial pressure. Thus, although nitroprusside and enoximone improved some indexes of early diastolic relaxation, they did not alter T_D or the peak rate of early diastolic filling. The left ventricular pressure-volume relation was shifted downward, indicating improved overall left ventricular distensibility, in only a minority of patients; the downward shifts resulted in part from a reduction in the external constraints to left ventricular filling. We conclude that enoximone and nitroprusside have similar effects on overall left ventricular diastolic performance in patients with severe heart failure, and, therefore, that enoximone has no specific beneficial effect on diastolic function.

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ABNORMALITIES of left ventricular diastolic function, including a reduced rate of left ventricular relaxation and decreased left ventricular compliance, have been identified in patients with congestive heart failure.1,2 These abnormalities may contribute to an elevation of left ventricular diastolic pressure and thus symptoms of congestion in these patients. Previous reports have demonstrated that vasodilators such as nitroprusside and nitroglycerin improve left ventricular distensibility, a property that may contribute to their beneficial effects in patients with heart failure.3–6 Recently, phosphodiesterase inhibitors, including milrinone and enoximone, have been introduced for the treatment of heart failure. Favorable effects of milrinone on left ventricular diastolic function have been reported,7 but the diastolic properties of enoximone are less fully characterized. Furthermore, since the phosphodiesterase inhibitors have both vasodilator and direct myocardial effects, it is not known to what extent their influence on diastolic function is direct and to what extent it is mediated by the effects of vasodilation on left ventricular loading conditions. To determine
whether the phosphodiesterase inhibitor enoximone has a specific, direct influence on left ventricular diastolic properties, we compared the effects of this agent and the pure vasodilator nitroprusside in 11 patients with severe congestive heart failure.

Methods

Patients. The study population consisted of nine men and two women with severe heart failure, due to coronary artery disease in seven patients and idio-pathic dilated cardiomyopathy in four patients (Nos. 5, 7, 8, and 10). Their mean (± SEM) age was 59 ± 3 years and all had NYHA class IV symptoms despite treatment with digoxin, diuretics, and vasodilators. All patients had systolic left ventricular dysfunction (mean left ventricular ejection fraction 0.20 ± 0.03; range 0.09 to 0.39). Informed consent was obtained from all patients.

Hemodynamic measurements. Patients underwent left and right heart catheterization without premedication 8 to 24 hr after discontinuation of digoxin, diuretics, and vasodilators. Systemic arterial pressure was measured with a micromanometer catheter (Millar) in eight patients and with a fluid-filled catheter in three patients (Nos. 1, 2, and 6). The following hemodynamic variables were recorded: heart rate (HR), right atrial pressure (RAP), pulmonary arterial pressure, pulmonary capillary wedge pressure (PCWP), left ventricular pressure, mean systemic arterial pressure (MAP), and, in the patients with micromanometer catheters, left ventricular dP/dt (by electronic differentiation). Cardiac index (CI) was calculated from the cardiac output obtained by the thermodilution technique.

The time constant of left ventricular relaxation, T1, was obtained from the micromanometer left ventricular pressure tracing according to the method of Weiss et al.: T1 = 1/slope of the regression line obtained by plotting the natural logarithm of left ventricular pressure (from the dicrotic notch pressure to 5 mm Hg greater than the end-diastolic pressure) versus time. The time constant was also calculated by the derivative method of Raff and Glantz: TD = 1/slope of a linear fit of negative dP/dt versus left ventricular pressure over the same interval. This method allows for a non-zero pressure asymptote PB.

Hemodynamic data were obtained at baseline, during constant infusion of nitroprusside, during a second control period at least 10 min after discontinuation of nitroprusside, and 10 min after administration of enoximone. Nitroprusside was infused at an initial dose of 25 μg/min and titrated to achieve a 10 to 15 mm Hg decrease in MAP (mean dose 95 ± 16 μg/min). Enoximone (0.5 mg/kg) was infused intravenously over 3 min, and this dose was repeated 15 min later in all but patient 1, who experienced angina after the first dose (mean dose 75 ± 6 mg).

Pressure-volume analysis. Left ventricular volume was calculated from supine gated blood pool images as previously described. Briefly, gated scans were acquired in the anterior and left anterior oblique views after labeling of red blood cells in vivo with technetium-99m. A time-activity curve of the left ventricle was constructed by a semiautomated edge detection method with a variable region of interest. Absolute left ventricular end-diastolic volume (LVEDV) at baseline was derived with a previously validated geometric biplane area-length method. Volumes at other time points in the cardiac cycle and after drug interventions were calculated as the baseline end-diastolic volume multiplied by the ratio of counts in a particular frame to counts in the baseline end-diastolic frame. The counts in scans obtained after the two drug interventions were corrected for differences from the baseline in acquisition time and frame interval and for physical and biological decay of the isotope.

The peak rate of left ventricular filling in early diastole was determined from a five-point algebraic differentiation of the smoothed time-activity curve (Medical Data Systems). The diastolic left ventricular pressure-volume relation was constructed by plotting left ventricular pressure (obtained by averaging five to 10 consecutive left ventricular pressure tracings from the midpoint of the gated scan acquisition) with simultaneous left ventricular volume at 10 to 20 msec intervals during diastole (from aortic valve closure to the peak of the R wave of the electrocardiogram). An improvement in overall left ventricular distensibility during infusion of nitroprusside or after administration of enoximone was defined as a left ventricular pressure difference of 3 mm Hg or more in overlap properties.

Statistics. All results are expressed as mean ± SEM. Overall comparisons were made by analysis of variance, and comparisons of group means by the Newman-Keuls test with a significance level of .05.

Results

Baseline measurements. Mean hemodynamic values are summarized in table 1. Baseline left ventricular end-diastolic pressure (LVEDP) was elevated at 26 ± 3 mm Hg, and baseline CI was depressed at 2.4 ± 0.2 liters/min/m². Values for LVEDV, maximum negative dP/dt, TL, and TD, and the peak rate of left ventricular filling (PFR) are shown in table 1. There were no significant differences between the two control periods in any of the measured or derived variables.

Effects of nitroprusside and enoximone on indexes of diastolic function. During infusion of nitroprusside (table 1), MAP fell from 85 ± 3 to 72 ± 2 mm Hg (p < .01), LVEDP fell from 26 ± 3 to 15 ± 3 mm Hg (p < .01), RAP fell from 9 ± 1 to 4 ± 1 mm Hg (p < .01), HR increased from 92 ± 4 to 98 ± 4 beats/min (p < .05), and CI increased from 2.4 ± 0.2 to 2.9 ± 0.2 liters/min/m² (p < .01). The fall in LVEDP was associated with a fall in LVEDV from 263 ± 22 to 238 ± 24 ml (p < .01). Td decreased from 84 ± 10 to 65 ± 8 msec (p < .01, figure 1); Td fell from 101 ± 10 to 90 ± 9 msec, but the difference was not statistically significant. There was no significant change in peak negative dP/dt or absolute PFR, although there was an increase in PFR divided by LVEDV.

Enoximone (table 1) produced no change in MAP, a decrease in RAP from 9 ± 2 to 5 ± 1 mm Hg (p < .01), an increase in HR from 91 ± 3 to 105 ± 4 beats/min (p < .01), and an increase in CI from 2.3 ± 0.2 to 3.2 ± 0.2 liters/min/m² (p < .01). LVEDV decreased from 26 ± 3 to 20 ± 4 mm Hg (p < .01), and LVEDV fell to 240 ± 26 ml (p < .01). Td decreased from 86 ± 12 to 61 ± 9 msec (p < .01, figure 1); Td decreased from 100 ± 11 to 86 ± 10 msec (p = NS), and peak negative dP/dt increased from 897 ± 101 to 1135 ± 134 mm Hg/sec (p < .01). The PFR increased significantly only when “normalized” for LVEDV.
Comparison of the effects of nitroprusside and enoximone (Table 1) shows that $T_L$ was shortened to a similar extent by nitroprusside and enoximone, whereas peak negative $dP/dt$ was significantly higher after enoximone ($p < .01$). LVEDP was lower for nitroprusside than for enoximone ($p < .01$) despite a similar LVEDV (figure 2).

**Effects on the diastolic pressure-volume relation.** Nitroprusside lowered LVEDP (measured as absolute intracavitary pressure) and LVEDV in four of 11 patients (Nos. 1, 2, 4, and 9) along an apparently unchanged diastolic pressure-volume relation, indicating no change in overall left ventricular distensibility (figure 3). In 3 patients (Nos. 3, 6, and 10) the relation was shifted downward so that the same left ventricular volume was associated with a lower left ventricular pressure during infusion of nitroprusside, indicating an improvement in overall left ventricular distensibility. These patients could not be distinguished from the other patients by any clinical or hemodynamic variable. However, reploting of the diastolic pressure-
volume relations with left ventricular pressure minus RAP (an approximation of “true” left ventricular transmural pressure) on the ordinate resulted in no downward shift in patient 3 and a decrease in the magnitude of the downward shift in patients 6 (figure 4) and 10. In the remaining four patients, LVEDV decreased sufficiently on nitroprusside to cause an absence of overlap of the diastolic pressure-volume relations, thereby precluding a meaningful comparison of the relations.

Enoximone resulted in leftward movement along an unchanged (patients 3, 4, 9, and 11) or nonoverlapping (Nos. 5, 7, and 8) diastolic pressure-volume relation in most patients (figure 3), whereas a downward shift occurred in only three patients (Nos. 2, 6, and 10). Adjustment of these curves for left ventricular transmural pressure by subtraction of the RAP abolished the downward shifts in all three patients, as illustrated for patient 6 in figure 4. Two patients (Nos. 1 and 9) experienced angina after administration of enoximone. In patient 1, angina was associated with an upward shift in the diastolic pressure-volume relation, indicating decreased left ventricular distensibility; in patient 9, there was no apparent upward shift (figure 3).

Discussion

Phosphodiesterase inhibitors such as amrinone, milrinone, and enoximone are mixed vasodilator and inotropic agents that exert a beneficial effect on hemodynamics in patients with heart failure. It has been shown

FIGURE 3. Left ventricular diastolic pressure-volume relations at baseline (●), during infusion of nitroprusside (○), and after administration of enoximone (★). Intracavitary left ventricular pressure is plotted on the ordinate and left ventricular volume on the abscissa. A downward shift in this relation, indicating improved left ventricular distensibility, was seen in three patients on nitroprusside (Nos. 3, 6, and 10) and in three patients on enoximone (Nos. 2, 6, and 10). Patients 1 and 9 experienced angina after enoximone, associated with an upward shift in the diastolic pressure-volume relation in patient 1.
that milrinone also improves indexes of left ventricular diastolic function in such patients. Since these drugs alter left ventricular preload and afterload, which in turn may influence diastolic function, it is not clear to what extent the effects of these drugs on diastolic function are due to vasodilation and to what extent they reflect a direct influence on the diastolic properties of the myocardium. We therefore compared the effects of enoximone on left ventricular diastolic function to those of the pure vasodilator nitroprusside in 11 patients with severe heart failure. Nitroprusside improved TL, the time constant of left ventricular relaxation, but had no effect on Td, peak negative dP/dt, or absolute PFR in early diastole. The left ventricular diastolic pressure-volume relation was shifted downward, indicating an improvement in overall left ventricular distensibility, in only three patients. Enoximone shortened TL to a similar degree. Although peak negative dP/dt increased with enoximone, there was no change in Td or absolute PFR. Left ventricular distensibility, as assessed by the diastolic pressure-volume relation, was also improved in only three patients.

**Indexes of early diastolic function.** Several previous studies have documented abnormalities in early diastolic function in patients with heart failure or a low ejection fraction.\(^1, 2, 14, 15\) The mean value of peak negative dP/dt in our patients (878 ± 96 mm Hg/sec) was similar to the value (1037 ± 115 mm Hg/sec) reported by Grossman et al.\(^1\) and the value (1060 ± 334 mm Hg/sec) reported by Hirota\(^2\) in patients with heart failure. Nitroprusside had no effect on this variable, as previously reported;\(^4\) enoximone increased peak negative dP/dt by 27%, which agrees closely with the previously reported increase produced by milrinone.\(^7\) Several investigators have demonstrated that peak negative dP/dt varies directly with afterload and, to a much lesser extent, HR.\(^16-18\) Karliner et al.\(^18\) found that an increase in HR from 99 to 162 beats/min in conscious dogs resulted in only an 8% increase in peak negative dP/dt, and Weisfeldt et al.\(^17\) were unable to demonstrate any significant change in peak negative dP/dt when HR was increased from 80 to 120 beats/min.\(^17\) Since MAP and peak left ventricular pressure were not significantly altered on enoximone and since HR increased only modestly, the observed increase in peak negative dP/dt probably resulted from either a direct effect on left ventricular myocardial relaxation or a secondary effect due to the improvement in contractile function.

Although TL as first measured by Weiss et al.\(^8\) appeared to be relatively load-independent, subsequent studies have suggested that TL varies directly with both preload and afterload and inversely with inotropic state.\(^9, 18, 19\) Thus the decrease in TL we observed during nitroprusside infusion most likely resulted from the decrease in left ventricular afterload (as assessed by the fall in MAP) and preload (as indicated by the fall in LVEDP and LVEDV). We cannot exclude the possibility, however, that early diastolic relaxation was improved directly by nitroprusside and that a corresponding increase in peak negative dP/dt was masked by a tendency of this index to decrease with the fall in afterload. Similarly, the decrease in Td after enoximone could have resulted from a direct effect of the drug on myocardial relaxation or could have been mediated by the decrease in preload and improvement in contractility. The time constant of exponential pressure decline was also calculated by the derivative method of Raff and Glantz\(^9\) (Td) to minimize potential errors in the measurement of left ventricular pressure due to pleural or pericardial pressure. Although there was a tendency for Td to decrease with both drugs, the changes were less uniform and not statistically significant.
Bonow et al.\textsuperscript{15} reported a left ventricular early diastolic filling rate of 1.3 ± 0.4 EDV/sec in patients with coronary disease and depressed ejection fraction (compared with 3.3 ± 0.6 EDV/sec in normal volunteers), which is in agreement with our baseline value of 1.3 ± 0.2 EDV/sec. An improvement in PFR “normalized” by dividing by LVEDV occurred in our patients with both nitroprusside and enoximone and has been reported to occur with milrinone.\textsuperscript{7} However, the absence of a significant change in absolute PFR suggests that this finding may reflect the decrease in LVEDV rather than any improvement in filling per se.\textsuperscript{20} Alternatively, an improvement in early diastolic filling could have been masked by a simultaneous fall in the driving force to filling as reflected by the decrease in PCWP. When PFR was normalized for stroke volume rather than LVEDV,\textsuperscript{21} there was no significant change with either nitroprusside or enoximone (table 1).

\textbf{Diastolic pressure-volume relations.} Nitroprusside produced a downward shift of the left ventricular diastolic pressure-volume relation in three of 11 patients with severe heart failure. Alderman and Glantz\textsuperscript{3} demonstrated a downward shift in three of seven patients on nitroprusside. Most of the patients had valvular heart disease and normal systolic left ventricular function (mean left ventricular ejection fraction 0.58). Brodie et al.\textsuperscript{4} observed a downward shift on nitroprusside in nine of 11 patients with symptoms of heart failure. However, these patients also differed substantially from our population, since no patient had coronary artery disease or severely impaired systolic function (mean left ventricular ejection fraction 0.57).

A downward shift in the diastolic pressure-volume relation during infusion of nitroprusside could have resulted from an improvement in the diastolic properties of the myocardium. However, since no direct myocardial effects of nitroprusside are known, an improvement in left ventricular distensibility may have resulted from an indirect effect such as a reduction in the external constraints to left ventricular distension. Alterations in right ventricular filling pressure have been shown to influence the left ventricular diastolic pressure-volume relation\textsuperscript{5, 6} via ventricular interaction within an intact pericardium.\textsuperscript{22, 23} Recently, Tyberg et al.\textsuperscript{24} demonstrated a correlation between RAP and left ventricular pericardial surface pressure, supporting the use of RAP as an index of the left ventricular external constraining pressure. The three patients in our study with improved distensibility on nitroprusside had high baseline RAPs of 14, 12, and 9 mm Hg. Since we did not measure pericardial pressure, we could not calculate true left ventricular transmural pressure in this study. However, adjustment of the diastolic pressure-volume relations for left ventricular transmural filling pressure as left ventricular intracavitary pressure minus RAP\textsuperscript{24} abolished the downward shift in patient 3 and diminished the shifts in patients 6 (as illustrated in figure 4) and 10. Finally, patient 11 had the highest baseline RAP (17 mm Hg) but did not have a downward shift on nitroprusside, suggesting that other mechanisms such as relief of ischemia or a reduction in contraction load\textsuperscript{25} may have contributed to the improvement in left ventricular distensibility.

After administration of enoximone, only three patients (Nos. 2, 6, and 10) exhibited downward shifts in the left ventricular diastolic pressure-volume relation. In contrast, Kerelakes et al.\textsuperscript{26} suggested that enoximine improved left ventricular distensibility in their patients based on a fall in mean PCWP with an unchanged LVEDV. This discrepancy may have resulted from their use of PCWP, which correlates only approximately with LVEDP, or from measuring left ventricular volume with a fixed region of interest by means of a nuclear probe, which may not be sufficiently sensitive to detect small changes in LVEDV, particularly in patients with regional wall motion abnormalities. Monrad et al.\textsuperscript{7} demonstrated a downward shift in the diastolic pressure-volume relation in a majority of patients on milrinone. LVEDV decreased in only two of their nine patients and actually increased in five patients. We observed a decrease in LVEDV in our patients on enoximone, which caused the fall in LVEDP to appear in most patients as a movement along an unchanged diastolic pressure-volume relation rather than as a shift to a lower relation. The difference in our findings may have been caused by differences in the study populations or in the methods used to measure left ventricular volume. The baseline RAP was higher in the study of Monrad et al.; consequently, more patients may have experienced improved distensibility secondary to a reduction in right-sided pressure. Although Monrad et al. also assessed left ventricular size by nuclear scan, they used a fixed region of interest to outline the left ventricle in each frame of the scan, whereas we used a variable region of interest to more reliably exclude the left atrium in each frame of the acquisition and to increase the sensitivity to detect small changes in volume. We cannot exclude the alternative possibility that milrinone and enoximone have different effects on left ventricular diastolic function.

The improvement in left ventricular distensibility in three of 11 patients after administration of enoximone may reflect an improvement in left ventricular relax-
ation, since peak negative dP/dt increased. A second possibility is that an improvement in left ventricular distensibility occurred as a result of a decrease in coronary perfusion pressure. This is unlikely, however, since both milrinone and enoximone have been reported to increase coronary blood flow. The most likely mechanism for improved distensibility on enoximone is a reduction in external constraints. Adjustment of the left ventricular diastolic pressure-volume relation for transmural left ventricular pressure by subtracting the RAP abolished the downward shifts in all three patients on enoximone, as illustrated for patient 6 in figure 4.

Angina occurred in two patients (Nos. 1 and 9) after administration of enoximone. As has been previously described in pacing- and exercise-induced angina, angina was associated in one of the two patients with an upward shift of the diastolic pressure-volume relation, indicating diminished left ventricular distensibility. Subclinical ischemia after administration of enoximone, caused either by the higher HR or by an increase in contractility, could have masked improved distensibility in other patients as well and may have accounted for the higher LVEDP on enoximone compared with nitroprusside. In this regard, when the diastolic pressure-volume relation was adjusted to reflect "true" left ventricular transmural pressure, two additional patients (Nos. 3 and 4) had upward shifts with enoximone and one patient (No. 4) had an upward shift with nitroprusside. All of these patients had coronary artery disease. It is possible that patient 4 experienced ischemia caused by coronary steal on nitroprusside.

A potential limitation of this study is that the time constraints imposed by left heart catheterization prevented the acquisition of a second baseline nuclear scan between the drug interventions. For this reason, left ventricular volume measurements after enoximone were compared with the first baseline acquisition. Since there were no significant changes between the two baseline periods in standard hemodynamic measurements, $T_1$, $T_p$, or peak negative dP/dt, it is unlikely that this introduced an important error. A second limitation of this study was that nitroprusside was given first to each patient; random drug sequencing was precluded in this left heart catheterization study by the relatively long half-life of enoximone. Finally, several patients had large volume changes after drug administration that resulted in nonoverlapping diastolic pressure-volume relations, and we were therefore unable to make meaningful comparisons of the relations in these patients.

**Summary.** The short-term administration of the phosphodiesterase inhibitor enoximone to patients with severe heart failure improved $T_1$ and peak negative dP/dt but shifted the left ventricular diastolic pressure-volume relation downward, indicating improved left ventricular distensibility, in only three of 11 patients. Similarly, nitroprusside shifted the diastolic pressure-volume relation downward in three patients. With both agents, the downward shifts were related in part to a decrease in right-sided pressures and thus a reduction in the external constraints to left ventricular distension. Thus the mixed inotropic-vasodilator agent enoximone has no greater influence on left ventricular diastolic function in patients with severe heart failure than does the pure vasodilator nitroprusside and therefore appears to have no hemodynamically important specific effect on diastolic properties of the myocardium.

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1220
THERAPY AND PREVENTION—CONGESTIVE HEART FAILURE

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