Inotropic Effect of Enoximone in Patients With Severe Heart Failure: Demonstration by Left Ventricular End-Systolic Pressure-Volume Analysis

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Left ventricular end-systolic pressure-volume analysis was employed to assess the inotropic effect of the phosphodiesterase inhibitor enoximone (formerly MDL-17,043) in nine patients with severe heart failure (New York Heart Association class IV symptoms, mean ejection fraction = 0.22). Left ventricular pressure-volume loops were constructed using high fidelity left ventricular pressure measured with micromanometer-tipped catheters and simultaneous left ventricular volume obtained by gated blood pool imaging. Afterload was reduced with the vasodilator nitroprusside to generate the baseline left ventricular end-systolic pressure-volume relation, a relatively load-independent measure of contractile function.

The intravenous administration of enoximone (mean dose 75 mg) shifted the end-systolic pressure-volume point upward and leftward from the baseline pressure-volume relation in eight of the nine patients, demonstrating a positive inotropic effect of this agent. The maximal rate of left ventricular pressure development (peak positive dP/dt) increased from 1,030 ± 142 to 1,381 ± 219 mm Hg/s (p < 0.01) on enoximone despite a significant decrease in preload (as assessed by left ventricular end-diastolic pressure and volume) and a small, insignificant decrease in mean arterial pressure. Two patients developed angina after enoximone administration; both patients had coronary artery disease and experienced a greater than 30% increase in heart rate-systolic blood pressure product.

Thus, enoximone has a significant inotropic effect in patients with severe heart failure. Like other inotropic drugs, it has the potential to increase myocardial oxygen demand and thereby precipitate ischemia.

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A new class of intravenous and oral agents has recently become available for the treatment of congestive heart failure (1–4). These agents, which include amrinone, milrinone and enoximone (formerly MDL-17,043), improve cardiac function by inhibiting phosphodiesterase F-III (5). Although both inotropic and vasodilator effects of these drugs have been documented in vitro, the inotropic effect has been more difficult to demonstrate in patients with heart failure, in part because of associated changes in left ventricular preload and afterload (6–8). In particular, the assessment of isovolumic phase indexes of left ventricular contractile function, such as the maximal rate of left ventricular pressure development (peak positive left ventricular dP/dt), has shown an improvement in these indexes in most (1,2,9) but not all (6) studies.

Recently, the end-systolic pressure-volume relation has emerged as a relatively load-independent measure of left ventricular contractile function (10–13). Borow et al. (14) used the end-systolic pressure-dimension relation derived from M-mode echocardiography to demonstrate a positive inotropic effect of milrinone in normal subjects. This technique cannot be extended to patients with severe heart failure, however, because most of these subjects have regional wall motion abnormalities, which preclude the use of M-mode echocardiography to assess chamber size.

The present study is the first to utilize the left ventricular end-systolic pressure-volume relation derived from left ventricular pressure-volume loops to assess the inotropic effect.
of a phosphodiesterase inhibitor, enoximone, in patients with severe heart failure. The study demonstrates that an increase in contractility contributes to the improved ventricular performance brought about by this agent.

Methods

Study patients. The study group comprised seven men and two women (mean age 60 ± 3 years) with severe congestive heart failure. All patients had New York Heart Association class IV symptoms despite treatment with digoxin, diuretics and vasodilators (including captopril in seven of the nine patients). The mean left ventricular ejection fraction was 0.22 ± 0.03. Six patients had coronary artery disease and three (Cases 5, 7 and 8) had idiopathic dilated cardiomyopathy. Seven patients had sinus rhythm and two (Cases 2 and 5) had atrial fibrillation. Informed consent was obtained from all patients.

Protocol. Digoxin, diuretics and vasodilators were discontinued 8 to 24 hours before catheterization and no premedication was given. Left heart catheterization was performed from the femoral approach using a micromanometer-tipped catheter (Millar) in six patients and a fluid-filled catheter in three patients (Cases 1, 2 and 5). Right heart catheterization was performed with a triple lumen balloon-tipped thermodilution catheter.

After baseline data were collected, nitroprusside infusion was begun at 10 to 25 μg/min and titrated to achieve a 10 to 15 mm Hg decrease in mean arterial pressure. Data were collected during the nitroprusside infusion (mean dose 82 ± 7 μg/min), and again at least 15 minutes after discontinuation of nitroprusside, when arterial pressure had returned to the baseline value. Enoximone (0.5 mg/kg body weight) was then infused intravenously over 3 minutes; this dose was repeated 15 minutes later in all but one patient (Case 1), who developed angina after the first dose. Measurements were made 10 to 20 minutes after the final enoximone dose.

Hemodynamic measurements. The following hemodynamic variables were recorded: heart rate (HR), right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), left ventricular pressure, mean systemic arterial pressure (MAP) and, in the patients with micromanometer-tipped catheters, left ventricular dP/dt (by electronic differentiation). Cardiac output (CO) was obtained by the thermodilution technique. Calculations of cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), stroke volume index (SVI) and stroke work index (SWI) were made using the following formulas: CI = CO/body surface area; SVR (dynes·s·cm⁻⁵) = 80(MAP – RAP)/CO; PVR = 80(PAP – PCWP)/CO; SVI (ml/m²) = CI/HR and SWI (g·m·m²) = (MAP – LV end-diastolic pressure) (0.0136) (SVI).

Gated blood pool imaging. After in vivo labeling of patient red blood cells with 20 mCi of technetium-99m, supine gated blood pool images were acquired in the anterior and left anterior oblique views; 200,000 counts were collected for the anterior view (16 frames) and 500,000 counts for the left anterior oblique view (32 frames). The acquisitions were normalized to the frame with the maximal number of counts and then filtered spatially and temporally. A time-activity curve of the left ventricle was constructed using a semiautomated edge detection method with a variable region of interest. Ejection fraction was calculated as stroke counts/end-diastolic counts.

Baseline left ventricular end-diastolic volume was derived from the anterior and left anterior oblique views using a previously validated geometric biplane area-length method (15, 16). Volumes at other time points in the cardiac cycle were calculated from the left anterior oblique scan as the end-diastolic volume multiplied by the ratio of counts in a particular frame to counts in the end-diastolic frame. During nitroprusside infusion and after enoximone administration, images were acquired only in the left anterior oblique view. Volumes 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. Care was taken to avoid patient and camera movement between treatment periods. The time-activity curves obtained after the two drug interventions were corrected for differences from the baseline in acquisition time and frame interval, and for physical and biologic decay of the isotope (17).

Pressure-volume loops. Left ventricular pressure readings from 5 to 10 consecutive beats were traced and digitized on a Summagraphics Bitpad interfaced to a VAX 780 computer. Average pressure was taken at the same frame interval as the volume images. Pressure-volume loops were then constructed by plotting these pressures with the corresponding volumes starting at a simultaneous time point (the peak of the R wave of the electrocardiogram).

Statistics. All results are expressed as mean ± SEM. For each measurement, overall comparison of the four treatment periods was made by analysis of variance; comparisons of group means were made using Neuman-Keuls test (18). Differences were considered significant if the probability (p) value was < 0.05.

Results

Baseline hemodynamics (Table 1). The baseline heart rate was 91 ± 4 beats/min and mean arterial pressure was 86 ± 4 mm Hg. Baseline pulmonary capillary wedge pressure and left ventricular end-diastolic pressure were elevated, and cardiac index was depressed. There were no significant differences between the two control periods in any of the measured or derived variables.
**Hemodynamic responses to nitroprusside and enoximone (Table 1, Fig. 1).** During sodium nitroprusside infussion (82 ± 7 μg/min), mean arterial pressure, right atrial pressure, pulmonary artery and capillary wedge pressures and systemic and pulmonary vascular resistances all decreased, whereas heart rate increased. Left ventricular end-diastolic pressure decreased from 24 ± 3 to 13 ± 3 mm Hg (p < 0.01) and cardiac index increased.

**Enoximone administration (75 ± 15 mg)** resulted in no change in mean arterial pressure, a decrease in systemic vascular resistance, a decrease in left ventricular end-diastolic pressure from 24 ± 4 to 18 ± 5 mm Hg (p < 0.05) and an increase in cardiac index. As with nitroprusside, right atrial pressure, pulmonary artery and capillary wedge pressures and pulmonary vascular resistance decreased, although the fall in pulmonary capillary wedge pressure was not statistically significant. Heart rate increased from 90 ± 4 to 104 ± 5 (p < 0.01) after enoximone.

**Comparison of the effects of nitroprusside with those of enoximone (Fig. 1)** shows that, for a similar decrease in systemic vascular resistance (26% after nitroprusside versus 22% after enoximone, p = NS), enoximone produced a larger increase in cardiac index (36 versus 15%, p < 0.05). The higher cardiac index with enoximone was due to both a higher heart rate and a higher stroke volume index. Left ventricular end-diastolic pressure decreased to a greater extent with nitroprusside than with enoximone (p < 0.05). Left ventricular end-diastolic volume decreased from 245 ± 21 to 221 ± 23 ml with nitroprusside (p < 0.01) and to 218 ± 25 ml with enoximone (p < 0.01). Stroke work index increased more with enoximone than with nitroprusside, although the increase was not statistically significant.

**Assessment of left ventricular contractile function.** Peak positive left ventricular dp/dt (measured in six patients) was unchanged with nitroprusside (1,025 ± 142 to 1,050 ± 144 mm Hg/s, p = NS), but increased 34% with enoximone (1,030 ± 142 to 1,381 ± 219 mm Hg/s, p < 0.01). Enoximone enhanced the contractile function of the left ventricle by increasing the dp/dt and the cardiac index, whereas nitroprusside produced no change in these variables.

### \( dP/dt \) and \( HR \)

\( dP/dt \) and \( HR \) increased more with enoximone than with nitroprusside, although the increase was not statistically significant. The increase in \( dP/dt \) with enoximone was 1025 ± 142 mm Hg/s, whereas the increase with nitroprusside was 1050 ± 144 mm Hg/s. The increase in \( HR \) with enoximone was 90 ± 4, whereas the increase with nitroprusside was 99 ± 5.

### Systemic resistances

The systemic resistances were also measured, and the results showed that enoximone produced a decrease in systemic resistance, whereas nitroprusside produced no change in systemic resistance.
This increase in dP/dt occurred despite a lower preload, as assessed by left ventricular end-diastolic pressure and volume, and a small but insignificant decrease in afterload, as estimated from mean arterial pressure. Ejection fraction increased slightly with both drugs, from 0.22 ± 0.03 in the control period to 0.25 ± 0.03 (p < 0.05) with nitroprusside and to 0.24 ± 0.03 (p < 0.01) with enoximone.

**Figure 2.** Left ventricular pressure-volume loops in the nine patients shown at baseline (●), during nitroprusside infusion (○), and after enoximone administration (X). The dashed lines indicate the hypothetical baseline pressure-volume relations determined by drawing a line tangential to the end-systolic portion of the loops at baseline and during nitroprusside infusion. In all patients except in Case 2, enoximone shifted the end-systolic portion of the pressure-volume loop upward or leftward, or both, from the baseline pressure-volume relation, indicating improved left ventricular contractile function.

Pressure-volume loops for all nine patients are shown in Figure 2. It is apparent that in all but one case (Case 2), the end-systolic pressure-volume point of the enoximone curve is shifted leftward and upward from a hypothetical line connecting the end-systolic points of the baseline and nitroprusside curves. This shift indicates an improvement in systolic performance which cannot be accounted for solely by a reduction in afterload, and therefore demonstrates enhanced left ventricular contractile function.

**Side effects.** Two patients (Cases 1 and 9) experienced typical angina shortly after receiving enoximone. For the entire group, the rate-pressure product (heart rate multiplied by systolic blood pressure) decreased slightly with nitroprusside, but increased 17% with enoximone because of a 16% increase in heart rate (Table 1). The two patients who developed angina had coronary artery disease, and they had the largest increases (>30%) in rate-pressure product (13,224 to 17,424 and 8,850 to 11,808 mm Hg-beats/min, respectively), compared with an average increase of 12% (range...
1 to 24%) in the other patients. No patient had symptomatic hypotension or ventricular arrhythmia.

**Discussion**

Although several studies (3,8,9,19) have shown that the acute administration of enoximone brings about hemodynamic improvement in patients with heart failure, it has been more difficult to demonstrate a positive inotropic effect of the drug in vivo because of its concomitant vasodilator effect. In this study, we analyzed the left ventricular end-systolic pressure-volume relation, a relatively load-insensitive index of left ventricular contractile function, to assess whether enoximone has a significant positive inotropic effect in patients with heart failure.

**Assessment of left ventricular contractile function.**

Previous investigations of the inotropic effect of phosphodiesterase inhibitors included measurements of peak positive left ventricular dP/dt, which was shown to increase 42, 30 and 15 to 23%, respectively, after administration of amrinone (1), milrinone (2,7) and enoximone (9,19) in patients with heart failure. We observed a similar 34% increase in peak positive dP/dt with intravenous enoximone. In contrast, Wilmshurst et al. (6) were unable to show any change in dP/dt in 14 patients with cardiomyopathy given amrinone, and concluded that the hemodynamic improvement that they observed was due to vasodilation. Although an increase in peak positive dP/dt is suggestive of an improvement in contractility, it may also be augmented by increases in heart rate or left ventricular preload or afterload (20,21). Because enoximone administration brought about a decrease in left ventricular preload (as assessed by left ventricular end-diastolic pressure and volume), a small but insignificant decrease in mean arterial pressure and only a small increase in heart rate, the observed increase in peak positive dP/dt most likely reflects an improvement in contractility.

**Ejection phase indexes of contractility have also been measured in patients receiving phosphodiesterase inhibitors.** Kereiakes et al. (22) demonstrated a decrease in left ventricular ejection time corrected for heart rate despite an increase in stroke volume. However, as they pointed out, this effect may also have been due to the decrease in arterial pressure. Baim et al. (2) reported a 27% increase in rest left ventricular ejection fraction after 6 months of treatment with oral milrinone. Borow et al. (14) demonstrated dose-dependent increases in left ventricular percent fractional shortening and rate-corrected velocity of fiber shortening with milrinone in men without heart disease. In the present study, the acute administration of intravenous enoximone to patients with heart failure resulted in a small increase in left ventricular ejection fraction, although it is not known whether this small increase is of clinical importance.

Recently, Ludmer et al. (23) administered milrinone directly into the left coronary artery of patients with heart failure. They showed that an increase in peak positive left ventricular dP/dt and stroke volume index could be achieved at intracoronary doses that had little systemic effect, indicating a positive inotropic effect of milrinone.

**End-systolic pressure-volume analysis.**

Definitive demonstration of the positive inotropic effect of the phosphodiesterase inhibitors has awaited the utilization of a relatively load-independent measure of left ventricular contractility. Suga et al. (10) showed that the end-systolic pressure-volume relation of the canine left ventricle is insensitive to changes in preload and that the slope of a line connecting several end-systolic pressure-volume points is sensitive to changes in contractility. End-systolic pressure-volume analysis has subsequently been extended to humans and has been shown to be a sensitive indicator of inotropic state independent of loading conditions (12,13,17,24).

Borow et al. (14) used an approximation of the end-systolic pressure-dimension relation derived from the dicrotic notch pressure of the calibrated carotid pulse tracing and minimal (end-ejection) left ventricular dimension from M-mode echocardiography to demonstrate a positive inotropic effect of milrinone in normal men. Konstam et al. (25) employed a similar approximation of the left ventricular end-systolic pressure-volume relation derived from systemic arterial dicrotic notch pressure and minimal (end-ejection) radionuclide left ventricular volume to suggest that amrinone had an inotropic effect in some patients with heart failure. End-ejection volume may differ from true end-systolic volume, however, particularly in the presence of mitral regurgitation (11). In contrast, Kereiakes et al. (22) were unable to show a significant increase in the ratio of peak systolic blood pressure to end-ejection volume index in patients treated with enoximone. Their inability to document an inotropic effect may have been due to the failure of peak systolic blood pressure to adequately correlate with end-systolic pressure, to the failure of nuclear probe measurements to accurately measure left ventricular volume, particularly in patients with regional wall motion abnormalities, or to differences between end-ejection and end-systolic volumes.

We have employed left ventricular pressure-volume loops to demonstrate that enoximone shifts the left ventricular end-systolic pressure-volume relation upward and leftward from the baseline end-systolic pressure-volume relation derived using the pure vasodilator nitroprusside. We believe that this is the strongest evidence to date that enoximone exerts a significant positive inotropic effect in patients with severe congestive heart failure.

In comparison with nitroprusside, enoximone produced a larger increase in cardiac index, despite a similar decrease in systemic vascular resistance. These findings are similar to those of other investigations comparing the hemodynamic effects of milrinone (7) or enoximone (8) with nitroprusside. The greater increase in cardiac index with enoximone was...
associated with both a higher heart rate and a greater stroke volume index.

**Side effects.** Two patients developed angina several minutes after the administration of enoximone. Both patients had multivessel coronary artery disease and experienced a >30% increase in rate-pressure product, compared with an average increase of 12% for the other seven patients. Packer et al. (26) reported on four patients who developed worsening manifestations of ischemia, including myocardial infarction in three, while receiving oral amrinone. Similarly, 3 of 20 patients treated with oral milrinone experienced more frequent anginal episodes (2). It is probable that ischemia occurred because of an increase in myocardial oxygen consumption resulting from the increases in heart rate, arterial pressure and contractility, which were not counterbalanced by a fall in wall tension due to a decrease in ventricular chamber size. Other potential mechanisms for the induction of ischemia, such as alterations in the distribution of regional coronary blood flow, were not assessed in this study.

Several investigations of the myocardial energetics of phosphodiesterase inhibitors have been carried out. Benotti et al. (27) studied nine patients given intravenous amrinone and showed a decline in arterial-coronary sinus oxygen difference, coronary blood flow and myocardial oxygen uptake. On the other hand, two studies (28,29) have shown small, but significant, increases in myocardial oxygen consumption in patients given intravenous enoximone. Furthermore, although Monrad et al. (30) reported no increase in mean rate-pressure product or myocardial oxygen consumption in 18 patients given oral milrinone, more than half of their patients had an increase in myocardial oxygen consumption, and this increase was >30% in 4 patients. Despite this increase in oxygen demand, none of the four patients experienced angina, probably because three of them had dilated cardiomyopathy without coronary artery disease and the fourth patient had undergone prior coronary revascularization.

**Limitations of the study.** The incorporation of left heart catheterization into the study protocol, while enabling us to construct pressure-volume loops for the left ventricle, imposed time constraints that limited the study in several ways. First, only two baseline pressure-volume loops were obtained for each patient, and the hypothetical end-systolic pressure-volume relation was constructed by drawing a line tangential to the two loops. This method is based on the assumption that the end-systolic pressure-volume relation is linear in patients with severe heart failure and can thus be reliably constructed from data with only two afterload states. Second, afterload was not varied with nitroprusside during enoximone administration; hence the full left ventricular end-systolic pressure-volume relation for enoximone was not derived. It is clear that, in eight of the nine subjects, the position of the end-systolic pressure-volume relation on enoximone is leftward or upward, or both, of the baseline relation, indicating an improvement in systolic performance not completely accounted for by a reduction in afterload. We did not determine, however, whether the slope of the end-systolic pressure-volume relation is altered by enoximone.

Also, because of time considerations, nuclear scanning was not performed during the second control period. Therefore, the radionuclide scan obtained after enoximone administration was compared with the scan from the first control period. However, because there were no differences between the control periods in any of the hemodynamic variables, it is unlikely that this resulted in a significant error.

Finally, we did not measure serum levels of enoximone in this study, and it is possible that the angina that occurred in two patients was associated with a high serum level. For this reason, the finding of angina after acute enoximone administration cannot be extended to chronic oral therapy, which may be associated with lower drug levels.

**Summary and implications for therapy.** In patients with severe heart failure, the acute administration of the phosphodiesterase inhibitor enoximone brings about an improvement in left ventricular contractile function. The inotropic effect of enoximone was demonstrated in this study by left ventricular end-systolic pressure-volume analysis, which is relatively insensitive to simultaneous changes in loading conditions. Angina occurs in some patients after the acute administration of intravenous enoximone; the relevance of this observation to long-term enoximone treatment is not known.

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**References**


