A Comparison of Three Phosphodiesterase Type III Inhibitors on Mechanical and Metabolic Function in Guinea Pig Isolated Hearts

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Little is known about of the comparative cardiac lusitropic and coronary vasoactive effects of type III phosphodiesterase inhibitors independent of their systemic circulatory effects. We hypothesized that phosphodiesterase inhibitors have dissimilar concentration-dependent effects on cardiac function and metabolism and that their coronary vasodilatory effects are solely dependent on flow autoregulation secondary to positive inotropic effects. Our aim was to compare the dose-response electrophysiologic, mechanical, vasodilatory, and metabolic properties of three clinically available phosphodiesterase inhibitors in isolated Langendorff perfused guinea pig hearts. We found that, over a range from 10^{-7} to 10^{-4} M, amrinone, enoximone, and milrinone each produced maximal concentration-dependent positive chronotropic (12%, 18%, 26%), inotropic (16%, 26%, 26%), and lusitropic (14%, 21%, 19%) effects. At clinical concentrations, all phosphodiesterase inhibitors increased heart rate, but only milrinone significantly enhanced contractility and relaxation (11%). Each phosphodiesterase inhibitor similarly increased contractility at its highest concentration; this was accompanied by an increase in oxygen consumption, which was matched by comparable increases in coronary flow and oxygen delivery. Coronary flow reserve was preserved at the highest concentration of each drug, indicating that an increased metabolic rate was responsible for the increase in coronary flow by each drug at each concentration. Over the concentrations examined, we conclude that each of the phosphodiesterase inhibitors does not directly promote coronary vasodilation and that milrinone has the most prominent effects on contractility and relaxation at clinically relevant concentrations.

(Anesth Analg 2006;102:1646–52)

The type III class of phosphodiesterase (PDE) inhibitors (PDIs), e.g., amrinone, enoximone, and milrinone, exert inotropic effects to slow or prevent cAMP breakdown by blocking type III specific PDE activity. The increase in cAMP levels in myocytes and vascular smooth muscle prolongs activation of protein kinases that produce combined inotropic and vasodilatory effects (1). Although there is controversy over indications for use of these PDIs (2,3), they have been used with some success not only for treatment of advanced heart failure but also for postoperative management after cardiac surgery in children and adults (2,4). PDIs have also been administered as a pharmacological bridging tool for heart failure patients awaiting heart transplant (5).

The pharmacological properties of PDIs have been described in different experimental models as well as in clinical studies. Although knowledge of the *in vivo* effects of PDIs are essential for proper clinical management of heart failure, it is also important to better understand and compare their direct effects on function and metabolism in isolated hearts to form a theoretical base for selecting them for clinical use. Prior studies have focused primarily on the cardiovascular effects of an individual PDI. The concentration-response functional and metabolic effects of these PDIs have not been directly compared in isolated hearts. We hypothesized that the three PDIs in clinical use, amrinone, enoximone, and milrinone, have different direct cardiac effects at equimolar concentrations. The aim of this study was

Accepted for publication January 31, 2006.

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DOI: 10.1213/01.ane.0000216290.74626.27

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0003-2999/06

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to directly compare functional and metabolic effects of these different PDIs, with special emphasis on their comparative vasodilatory and contractile effects.

Methods

With approval of the Animal Studies Committee of the University of Heidelberg, 36 English short-haired albino guinea pigs (242 ± 7 g) were injected IP with 10 mg of ketamine and 1000 U of heparin. After decapitation and sternotomy, the heart was rapidly excised during continuous retrograde aortic perfusion with a cold, oxygenated and modified Krebs-Ringer solution, saturated with 95% O_2 and 5% CO_2, and transferred to a Langendorff apparatus (Hugo Sachs Electronic KG, March-Hugstetten, Germany). A description for this model and the surgical procedures have been previously reported in detail (6,7). The Krebs-Ringer's solution contained (in mM): Na^+ 140; K^+ 4.5; Mg^{2+} 1.2; Ca^{2+} 2.5; Cl^- 134; HCO_3^- 15.5; $H_2PO_4^-$ 1.2; EDTA (ethylene-diamine-tetraacetic) 0.05; glucose 11.5; pyruvate 2; mannitol 10; and insulin 5 U/L. Hearts were suspended in a temperature-regulated chamber; perfusate and heart temperatures were maintained at 37.0°C ± 0.2°C throughout the experiment.

A thin, saline-filled latex balloon (Hugo Sachs Electronic KG, March-Hugstetten, Germany) was inserted into the left ventricle and was attached to a metal cannula. The connection of this cannula to a pressure transducer (Gould-Statham P23; Gould Electronics, Elk Grove, IL) provided for measurement of isovolumetric systolic left ventricular pressure development. Balloon volume was adjusted to maintain an initial diastolic left ventricular pressure of 0 mm Hg during the control period so that any increase in diastolic left ventricular pressure reflected an increase in left ventricular wall stiffness or diastolic contracture. Once balloon volume was set it remained constant throughout the experiment. The maximal and minimal rate of force development (+/−dLVP/dt) was determined from the left ventricular pressure (LVP) signals with an electronic differentiator and used as indices of cardiac contractility and lusitropy. Two pairs of bipolar silver electrodes (Teflon-coated silver; diameter 125 μm; Cooner Wire, Chatsworth, CA) were attached to the right atrium and the pulmonary conus. Spontaneous atrial heart rate (HR) was determined from the right atrial beat-to-beat interval. Atrioventricular conduction time (AVCT) was analyzed from the right atrial to the right ventricular pulmonary conus beat-to-beat interval by an electronic timer. AVCT includes conduction not only through the atrioventricular node but also across Purkinje fibers and ventricular myocytes.

Coronary inflow was measured at a constant pressure of 55 mm Hg (75 cm fluid column) by an inline ultrasound inflow meter (Research Flowmeter T 106; Transonic System Inc., Ithaca, NY). After ligating both venae cavae, coronary sinus effluent was collected using a small catheter placed into the right ventricle through the pulmonary artery.

Oxygen tension and electrolytes in the coronary inflow and outflow were measured using a self-calibrating gas analyzer (Radiometer ABL-2; Metron Chicago, Des Plaines, IL). Mean aortic inflow pH, CO_2 tension (Pco_2), and oxygen tension (Po_2) were 7.4 ± 0.4, 35 ± 2 mm Hg and 665 ± 37 mm Hg (mean ± SEM), respectively. Oxygen delivery (DO_2), percentage oxygen extraction (O_2Ext), and myocardial oxygen consumption (MVO_2) were calculated as described previously (6). The average wet weight of all hearts was 1.70 ± 0.04 g. AVCT, HR, LVP, positive and negative first derivatives of LVP (dLVP/dt), and coronary inflow were continuously measured, displayed on a screen, and recorded digitally on a hard drive for 30 s. All measurements were taken during the last minute of each 15-min experimental period for statistical analysis.

To determine maximal coronary flow reserve, adenosine was injected (0.2 mL of a 200 μM stock solution) directly into the aortic root cannula during the initial control period. The heart was allowed to stabilize for at least 30 min before initial control measurements were taken. After stabilization, 6 hearts in which coronary flow was <5 mL · min^{-1} · g^{-1}, contractility (+dVLP/dt <1000 mm Hg) was low, HR was slow (<200 bpm), or frequent ventricular dysrhythmias occurred were excluded from the study.

The hearts were randomly assigned by lottery to 3 groups (10 hearts each) and received amrinone (Wincoram®, Sanofi Winthrop, Munich, Germany), enoximone (Perfan®; Hoechst, Frankfurt, Germany), or milrinone (Corotrop®; Sanofi Winthrop, Munich, Germany). Lower concentrations were made from 10^{-4} M stock solutions. The concentrations tested in our study (10^{-7} to 10^{-4} M), which are equivalent to 0.019–19 μg/mL amrinone, 0.025–25 μg/mL enoximone, and 0.021 – 21 μg/mL milrinone, correspond to approximate therapeutic plasma-free values (corrected for plasma protein binding, in %) of 1.7 – 2.4 · 10^{-5} M (20%–45%) amrinone, 3.0–4.5 · 10^{-6} M (55%–70%) enoximone, and 0.4–1.0 · 10^{-6} M (50%–80%) milrinone (8–10). Concentrations that were smaller and larger (amrinone: 1 · 10^{-7} to 5 · 10^{-6} M and 5 · 10^{-5} M to 1 · 10^{-4} M; enoximone: 1 · 10^{-7} to 1 · 10^{-6} M and 1 · 10^{-5} to 1 · 10^{-4} M; and milrinone: 1 · 10^{-7} and 1 · 10^{-6} to 1 · 10^{-4} M) than estimated clinical plasma concentrations were examined to compare drug responses.

Each heart was perfused, in randomized order, at concentrations of 10^{-7} to 10^{-4} M with one of these drugs for a period of 15 min. There was a 15-min drug-free washout period after perfusion at each drug

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Table 1. Average Baseline Values for Three Phosphodiesterase Inhibitors on Cardiac Function.

	Amrinone	Enoximone	Milrinone
Heart rate (bpm)	238 ± 7	224 ± 5	233 ± 4
+dLVP/dt (mm Hg·s^{-1})	1191 ± 24	1129 ± 26	1115 ± 18
−dLVP/dt (mm Hg·s^{-1})	−950 ± 17	−910 ± 20	−909 ± 17
Coronary flow (mL·min^{-1}·g^{-1})	6.6 ± 0.3	6.8 ± 0.5	6.9 ± 0.4
DO_2/MVO_2	2.1 ± 0.1	2.2 ± 0.1	2.1 ± 0.2

There were no statistical baseline differences for the amrinone, enoximone, and milrinone groups after stabilization. Data are the means of 10 experiments per drug with errors representing the SEM.

concentration. After the washout reading, adenosine was again given to assess any change in maximal coronary flow. Hearts were included in this study only if maximal coronary flow at the beginning and at the end of each experiment was not significantly different.

Raw data from each functional and metabolic variable were compared by analysis of variance with repeated measures. If F tests were significant, Student-Newman-Keuls' tests were used to compare absolute group means for each variable measured at the same concentration and individual drug concentrations (and washout, WASH) against the initial control. $P < 0.05$ was considered to be statistically significant. For better visualization all raw data in the figures were normalized to percentage change from control and were displayed as means ± SE of the means (SEM) rather than SD. Because the sample size for each drug group was identical the SD is proportional to the SEM.

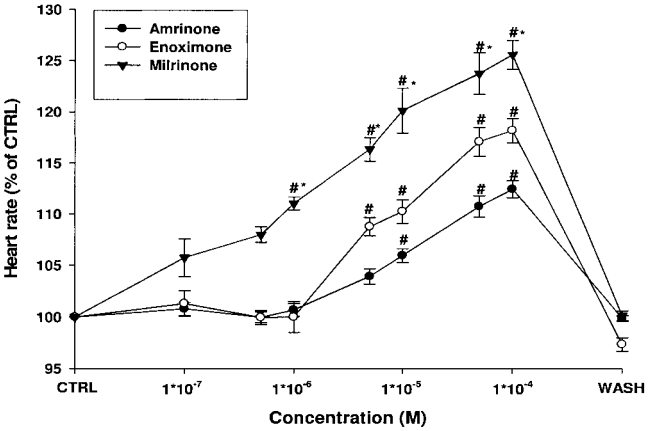

Figure 1. Comparative effect of amrinone, enoximone, and milrinone on heart rate in guinea pig isolated hearts. Milrinone was more potent than amrinone and enoximone at equimolar concentrations. For control values, only the first (control) and the washout (WASH) periods are displayed. #$P < 0.05$ amrinone, enoximone, and milrinone versus control; *$P < 0.05$ milrinone versus amrinone and enoximone. Data are the means of 10 experiments per drug (normalized to percentage change from control), with vertical lines representing the SEM.

Results

Control values (CTRL) showed no statistical differences among the groups after stabilization (Table 1). Post-control values (WASH) were not significantly different from the initial control values for any measured variable.

Each drug increased HR as a function of increasing concentrations (Fig. 1). At $1 \cdot 10^{-4}$ M, HR was increased maximally by 12% ± 2% with amrinone, by 18% ± 1% with enoximone, and by 26% ± 1% with milrinone ($P < 0.05$ versus amrinone and enoximone). Only milrinone significantly increased the HR at smaller clinical concentrations ($1 \cdot 10^{-6}$ M). At larger concentrations ($1 \cdot 10^{-5}$ – $1 \cdot 10^{-4}$ M) each drug significantly increased HR. Milrinone was significantly more potent than amrinone and enoximone at $1 \cdot 10^{-6}$ – $1 \cdot 10^{-4}$ M. Washout values were not significantly different from the initial control values. No drug concentration had any significant effect on altering AVCT; hearts remained in sinus rhythm and there were no ventricular dysrhythmias other than an occasional preventricular excitation.

As shown in Figure 2 amrinone, enoximone, and milrinone each enhanced cardiac contractility (+dLVP/dt). Only milrinone increased +dLVP/dt significantly at smaller concentrations ($5 \cdot 10^{-7}$, $1 \cdot 10^{-6}$, and $5 \cdot 10^{-6}$ M); at $1 \cdot 10^{-4}$ M the maximal increases in contractility were 26% ± 3% for milrinone, 26% ± 3% for enoximone, and 16% ± 1% for amrinone. Similar to their effects to enhance contractility, amrinone, enoximone, and milrinone each exhibited a lusitropic effect as shown in Figure 3 by maximal increases in −dLVP/dt of 14% ± 1%, 21% ± 3% and 19% ± 4%, respectively. At clinical concentrations ($1 \cdot 10^{-6}$ and $5 \cdot 10^{-6}$ M), however, only milrinone exhibited a significant lusitropic effect that was significantly more potent than that of amrinone and enoximone at $5 \cdot 10^{-6}$ and $1 \cdot 10^{-5}$ M.

Coronary flow increased significantly to a maximum of 10.1 ± 1.1 mL · min^{-1} · g^{-1}, a 47% ± 6% increase, for milrinone at $5 \cdot 10^{-5}$ M (Fig. 4). For amrinone and enoximone maximal flow was increased less at the same concentration, by 23% ± 4% and 26% ± 5%, respectively. For amrinone and enoximone, the absolute increases in coronary flow were not significant at any concentration. Maximal flow responses to bolus adenosine administration before and after drug concentration studies were increased significantly (*P*

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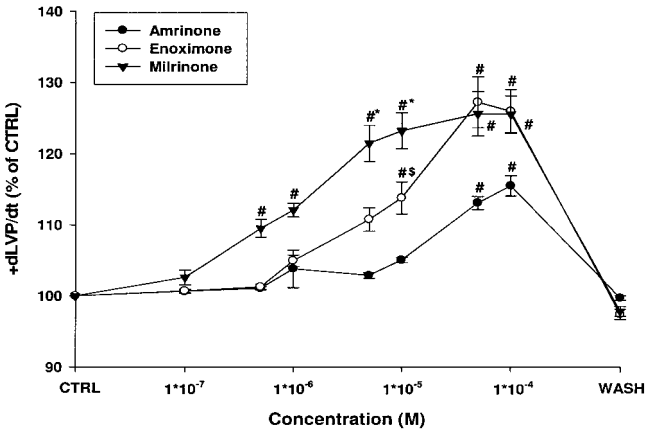

Figure 2. Comparative effects of amrinone, enoximone, and milrinone on +dLVP/dt in guinea pig isolated hearts. Each drug increased contractility, but milrinone was the most potent. For control values, only the first (CTRL) and the washout (WASH) periods are displayed. #$P < 0.05$ amrinone, enoximone and milrinone versus control; *$P < 0.05$ milrinone versus amrinone and enoximone; \$$P < 0.05$ enoximone versus amrinone. Data are the means of 10 experiments per drug (normalized to percentage change from control), with vertical lines representing the SEM.

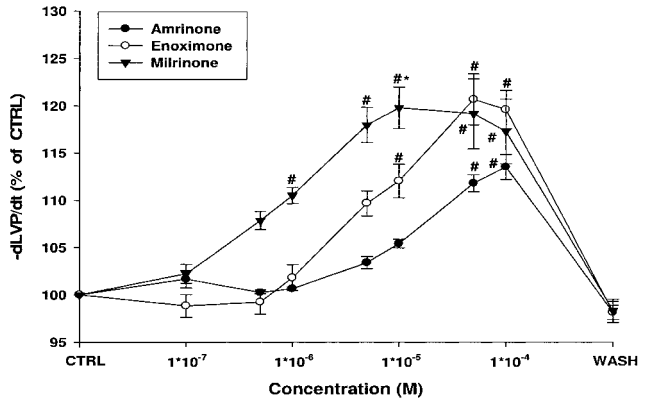

Figure 3. Comparative effects of amrinone, enoximone, and milrinone on −dLVP/dt. Amrinone, enoximone, and milrinone increased relaxation, but milrinone was the most potent. Amrinone, enoximone and milrinone increased −dLVP/dt by 14% ± 1%, 21% ± 3%, and 19% ± 4%, respectively. #$P < 0.05$ amrinone, enoximone, and milrinone versus control; *$P < 0.05$ milrinone versus amrinone and enoximone. Data are the means of 10 experiments per drug (normalized to percentage change from control), with vertical lines representing the SEM.

< 0.05 for each drug versus baseline) to 22 ± 1 and 21 ± 1 mL · min^{-1} · g^{-1} for amrinone, 21 ± 1 and 20 ± 1 mL · min^{-1} · g^{-1} for enoximone, and 21 ± 1 and 21 ± 1 mL · min^{-1} · g^{-1} for milrinone ($P > 0.1$ for each drug after versus before).

A significant and parallel increase in oxygen demand was observed after administration of amrinone, enoximone, and milrinone ($5 \cdot 10^{-5}$ M and $1 \cdot 10^{-4}$ M). At concentrations less than $5 \cdot 10^{-5}$ M enoximone and milrinone significantly increased MVO_2 (data not displayed). At $5 \cdot 10^{-5}$ M MVO_2 values were 79 ± 3 μL · min^{-1} · g^{-1} (19% ± 4% increase; $P < 0.05$) for

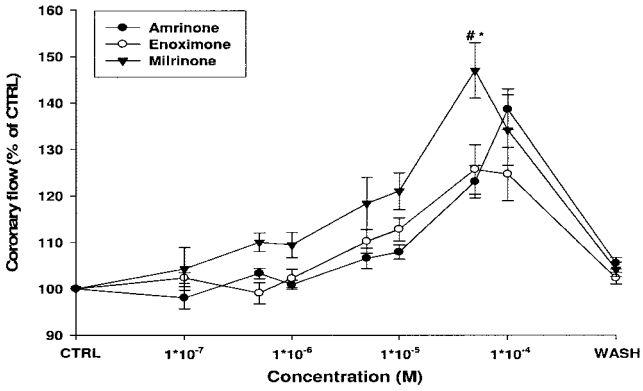

Figure 4. Comparative effects of amrinone, enoximone, and milrinone on coronary flow. Only milrinone increased flow significantly. Statistical symbols used are: #$P < 0.05$ milrinone versus control; *$P < 0.05$ milrinone versus amrinone and enoximone. Data are the means of 10 experiments per drug (normalized to percentage change from control), with vertical lines representing the SEM.

milrinone versus 71 ± 2 μL · min^{-1} · g^{-1} (12% ± 1% increase, $P < 0.05$) for amrinone and 76 ± 4 μL · min^{-1} · g^{-1} (21% ± 3% increase, $P < 0.05$) for enoximone. With the drug-induced increase in MVO_2, oxygen supply increased proportionally so that oxygen extraction (not shown) and DO_2/MVO_2 (Fig. 5) values were not significantly different among the drugs at any concentration. These indices indicate that there was no direct vasodilatory effect of these drugs at any concentration.

Discussion

This is the first study to directly compare electrophysiologic, mechanical, and metabolic effects of amrinone, enoximone, and milrinone in the isolated heart at increasing equimolar concentrations. We found that each PDI exerted cardiac positive chronotropic, vasodilatory, inotropic, and lusitropic effects in a dose-dependent manner. We found no evidence of dromotropic or dysrhythmogenic effects for any drug. At clinical concentrations, each drug showed significant increases in HR, but only milrinone significantly increased contractility and enhanced relaxation. The drug-induced increases in HR and contractility were balanced by relative changes in oxygen demand and oxygen supply. Compared with amrinone and enoximone, at larger concentrations milrinone significantly increased coronary flow and therefore oxygen supply; this was matched by an increase in MVO_2. Amrinone and enoximone caused lesser increases in oxygen supply and MVO_2 at higher concentrations. Coronary autoregulation presumably remained intact because coronary vasodilatory responsiveness was higher during adenosine administration than during PDI administration, so that maximal flow and oxygen supply by the PDIs were not limiting. Our study thus indicates

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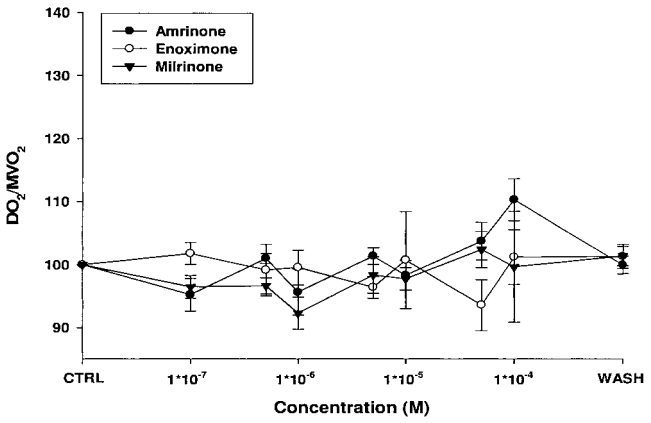

Figure 5. Comparative effects of amrinone, enoximone, and milrinone on the oxygen supply to demand ratio (DO_2/MVO_2). None of these drugs increased DO_2/MVO_2 from the control values. Data are the means of 10 experiments per drug (normalized to percentage change from control), with vertical lines representing the SEM.

that none of the three PDIs is a direct coronary vasodilator at comparable concentrations in this model. The increase in flow by milrinone is a result of autoregulation of coronary flow secondary to the increase in cardiac metabolic rate.

The modified isolated Langendorff heart is a well established *ex vivo* preparation to examine direct effects of drugs independent of neural, hormonal, and preload and afterload conditions (6,7). Effects of single concentrations of individual PDIs have been investigated in *in vitro* models and *in vivo* studies (8–10). The Langendorff cardiac model offered us the possibility to focus on and compare the direct cardiac effects of the primary active compounds, independent of active metabolites. The range of concentrations of amrinone, enoximone, and milrinone used in this study are similar to those reported in other in *vitro* and *in vivo* studies (7–11). In contrast to amrinone and milrinone, enoximone has active metabolites, especially enoximone sulfoxide (12). The potency of enoximone sulfoxide has been described as only one seventh that of enoximone and effective plasma concentrations are achieved in the clinical setting only later after administration (4,12).

Electrophysiological effects of these PDIs have been well examined in single studies. Amrinone, enoximone, and milrinone were each shown to increase HR *in vitro* and as well as *in vivo* (7–11). Our findings of positive chronotropic effects agree with those studies. Because PDIs have a systemic vasodilatory effect *in vivo*, all or a portion of the HR increase could arise from adrenergic stimulation via a baroreflex mechanism secondary to decreased venous return to the heart. But as this model is unaffected by extrinsic influences, a direct chronotropic effect was demonstrated by each of these drugs. Milrinone, especially at clinically relevant concentrations, is a more potent chronotropic drug than are enoximone and amrinone, as already described in experimental models (13,14). Clinical studies (8–10) show some differences from *in vitro* studies. One factor may be species-related differences in PDE activity (15). Interaction with other medications and a differential vasodilatory effect of PDIs at different concentrations (16) may also explain the major differences observed *in vivo* and *in vitro* results.

The effects of these PDIs on altering AVCT is not conclusive across several models because in different studies PDIs are reported to cause no change or to produce positive or negative dromotropic effects (7–11,14). Although we did not control for a possible HR effect on AVCT, we found no direct change in AVCT time by any drug. Differences between our study and those of others are likely multifactorial; in *vitro* versus in *vivo*, species, heart size, drug concentration, and in clinical studies, concomitant medications (e.g., β-adrenergic blocker, digitalis or catecholamine) (17) could easily account for differences. It appears from our study that these drugs have little or no direct dromotropic effect.

We did not observe any direct dysrhythmogenic effects by these PDIs; this agrees with several other studies (7,9,14). Dysrhythmias have been observed in experimental studies in which larger concentrations of PDIs were given (11). In one clinical study of 24-hour analysis of Holter electrocardiogram recordings there was no significant increase in the incidence of ventricular dysrhythmias by PDIs (17). An increase in dysrhythmias was not observed after cardiopulmonary bypass. Joseph et al. (14) and others (7,9,14) observed that the dysrhythmogenic potential of milrinone was less than that of digitalis or epinephrine, alternative drugs often used in the therapy of decompensated chronic heart failure.

In agreement with findings in other experimental models, we found that each PDI directly increased contractility in a dose-dependent manner (7,13,14). However, milrinone was approximately 10 times more effective than enoximone and 100 times more effective than amrinone in increasing +dLVP/dt by approximately 12%. The potency difference between amrinone and milrinone is better understood (18) than the difference between these two PDIs and enoximone. The relative potencies of these drugs approximate those of other less detailed and comparative *in vitro* studies (13,14), but care must be taken in directly comparing potencies derived from our study to those evaluated from clinical investigations (2).

Another focus of this study was to directly compare the PDIs for lusitropic effects, which had not been systematically examined before this study (19). In the few reported studies on cardiac relaxation, few of the *in vitro* studies used a whole heart model and none compared these PDIs with each other (19,20). In intact animal studies, the vasodilatory effect of a PDI can

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influence ventricular relaxation by reducing cardiac afterload (16). In this respect, the Langendorff model with constant preload and afterload allows examination of a direct lusitropic effect. Amrinone, enoximone, and especially milrinone at smaller concentrations increased peak −dLVP/dt. With a focus on clinically relevant concentrations, however, only milrinone significantly enhanced relaxation. Because diastolic dysfunction is an important factor in the pathophysiology of diverse forms of heart failure (16), the relaxation property of PDIs is an important pharmacological tool for their use in the clinical setting. This lusitropic property of PDIs, especially milrinone, makes them a useful adjunct for treating patients with congestive heart failure (17) and as a pharmacologic bridge support after cardiac surgery (2,4).

Vasodilatory effects have been described for PDIs (7,19). Our model allows examination of a direct coronary vascular effect independent of autoregulation. Amrinone, enoximone, and milrinone each tended to increase coronary flow but this was only significant for milrinone at the higher concentrations. This lack of a significant increase in coronary flow for amrinone and enoximone was offset by a lesser oxygen extraction and oxygen consumption because of their smaller positive chronotropic and inotropic effects. Consequently, the oxygen supply to demand ratio remained constant. Because these hearts exhibited sufficient coronary reserve before and after treatment with each of the PDIs, this indicates that coronary autoregulatory capability was intact (21) as also suggested by others (7). In contrast to amrinone and enoximone, milrinone significantly increased coronary flow and enhanced oxygen delivery to match the increase in oxygen demand. Thus our study demonstrates that even at higher concentrations, milrinone, as well as the other two PDIs, is not a direct coronary vasodilator in this model.

In addition to coronary flow autoregulation and enhanced metabolic effects, other direct effects of PDIs could influence oxygen balance. The lusitropic effect may influence myocardial oxygen supply and acceleration of the ventricular relaxation phase may prolong the coronary perfusion period. Because oxygen demand depends on HR, contractility, and wall tension, the systemic vasodilatory effect of PDIs has been proposed to reduce ventricular wall stiffness, thereby reducing oxygen demand (22,23).

A potential limitation of our study is that hearts were perfused with crystalloid solution. This can affect vascular reactivity so that the results obtained with flow autoregulation may be qualitatively different in blood-perfused hearts. The level of oxygen consumption can be different *in vitro* (7,20) and *in vivo* (24) depending on the model used, working or nonworking, perfusion with hemoglobin, red cells, or crystalloid perfusate, the plasma protein concentration, drug concentration, and age (25). Another potential limitation is that the range of effective clinical concentrations is difficult to discern and compare in an isolated heart model. Also, each PDI has a different binding activity to plasma protein and the hearts are perfused with colloid-free solution.

In summary, this is the first study to directly compare cardiac effects of three clinically used PDIs, amrinone, enoximone, and milrinone at increasing equimolar concentrations. We confirmed, in a dose-dependent manner, the positive chronotropic, inotropic, and lusitropic effects of the PDIs. Moreover, at the concentrations used neither dromotropic nor dysrhythmogenic effects could be detected. Although each PDI showed marked lusitropic effects at larger concentrations, only milrinone significantly increased cardiac relaxation at clinically used concentrations. These specific effects may also contribute to a balance of oxygen supply to demand. An important facet of this study was to determine if PDIs are direct coronary vasodilators independent of an autoregulatory flow effect. Although the increase in oxygen consumption was greater for milrinone than for enoximone and amrinone, the increase in flow with milrinone at high concentrations was attributable to the need to match oxygen supply to oxygen demand, implying that neither milrinone nor the other drugs are direct coronary vasodilators. We conclude that these drugs have similar direct cardiac properties although their potencies are different, with milrinone being the most potent of the three PDIs on HR, contractility, and relaxation.

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