Amrinone Reverses Cardiac Depression and Augments Coronary Vasodilation with Isoflurane in the Isolated Heart


Amrinone is a positive inotropic and vasodilatory agent and may be administered during anesthesia with isoflurane. The authors' aims were 1) to examine if amrinone produces coronary artery vasodilation through an increase in metabolic demand or through a direct vasodilatory effect; or through both and 2) to test if amrinone attenuates cardiac depression and enhances coronary artery vasodilation produced with exposure to isoflurane. The effects of these drugs were examined in 11 isolated perfused guinea pig hearts. Variables measured were: heart rate (HR), atrioventricular conduction time (AVCT), isovolumetric peak left ventricular pressure (LVP), coronary flow, percent O2 extraction, myocardial O2 consumption (MVO2), and the ratio of O2 delivery (Do2) to MVO2. Each heart was exposed for 10-min periods to 10, 50, 100, and 500 μg amrinone alone, and to 0.5 or 1% isoflurane before, during, and after amrinone. Initial control values were: heart rate 216 ± 5 beats per min; AVCT 56 ± 1 ms; peak LVP 86 ± 3 mmHg; coronary flow 6.5 ± 0.3 ml·min⁻¹·g⁻¹ (11.4 ± 0.7 ml·min⁻¹·g⁻¹ with adenosine bolus); percent O2 extraction 52 ± 5%; Do2 107 ± 3 μl·min⁻¹·g⁻¹; MVO2 56 ± 4 μl·min⁻¹·g⁻¹; and Do2/MVO2 1.75 ± 0.08. Amrinone 500 μg alone increased (P < 0.05) heart rate by 9%, LVP by 13%, coronary flow by 18%, and MVO2 by 23%; AVCT decreased by 3%. Isoflurane, 0.5 and 1 vol%, decreased heart rate by 5 and 8%, LVP by 7 and 13%, and percent O2 extraction by 11 and 18%; AVCT increased by 4 and 5%; coronary flow by 11 and 20%; and Do2/MVO2 by 12 and 18%, respectively. MVO2 was not altered (P > 0.05) by isoflurane alone and percent O2 extraction and Do2/MVO2 were not altered by amrinone alone. In combination, isoflurane significantly shifted the amrinone response curves, parallel and upward for AVCT and coronary flow and parallel and downward for heart rate and LVP. Isoflurane did not significantly shift the MVO2 response curve for amrinone. Percent O2 extraction decreased, and Do2/MVO2 increased with isoflurane in combination with only the two highest concentrations of amrinone. 500 μg amrinone completely counteracted the changes in heart rate, AVCT, and LVP resulting from 1% isoflurane. These results show that amrinone is a mild, directly acting, positive chronotropic and inotropic agent that produces concomitant increases in MVO2 in the isolated heart. Isoflurane, a negative chronotropic and inotropic agent, produces purely inhibitory effects with amrinone on heart rate, AVCT, and LVP, and purely additive effects with amrinone on coronary flow (and Do2). Moreover, amrinone increases coronary flow because of an increase in MVO2, whereas isoflurane increases coronary flow by decreasing Do2 without decreasing MVO2. This indicates that isoflurane, a directly acting coronary artery vasodilator, accentuates the compensatory coronary vasodilatory effect of amrinone that results from increased MVO2.

(Am J Cardiol 1979; 44: 1176–8) (Key words: Anesthetics: volatile; isoflurane. Animal: guinea pig. Pharmacology: amrinone. Heart: coronary flow; electrophysiology; isolated; myocardial oxygen consumption; left ventricular pressure.)

AMRINONE, a bipyridine derivative, is a relatively new inotropic and vasodilatory agent first described in experimental and clinical studies in 1979.1–3 Its precise mechanism of action has not yet been fully elucidated. It is unique in that it functions independently of the β1-adrenergic receptor and is not a glycoside.2 Studies in vitro indicate that the drug probably inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase fraction III (PDE III) in heart muscle to produce its positive inotropic and chronotropic effect.4,5,8,10 This resulting change in cellular levels of cAMP alters the uptake of Ca2+ from the sarcolemma, its release from sarcoplasmic reticulum, and its delivery to the contractile system.6–8

In addition to its positive inotropic and chronotropic effect, amrinone dilates pulmonary and systemic vascular beds.2,8,10 This vasodilator activity has been attributed to nonspecific inhibition of smooth muscle contractility at multiple sites,11 to an increase in cAMP, which facilitates Ca2+ uptake by sarcoplasmic reticulum,11 and to potentiation of the vasodilatory action of adenosine.12 Whether amrinone increases coronary flow beyond the metabolic need of the heart has not been adequately examined.

Whether the positive inotropic effect of amrinone is a direct cardiac effect or is an effect secondary to changes in venous return or peripheral vascular resistance remains controversial. The majority of clinical investigators have found a positive inotropic effect on the basis of increased cardiac output and left ventricular pressure (LVP) development, when accompanied by a decrease in preload volume.1,2,6,10 In contrast, other clinical investigators have not been able to establish any direct positive inotropic effects of amrinone on heart rate, AVCT, and LVP, and purely additive effects with amrinone on coronary flow (and Do2). Moreover, amrinone increases coronary flow because of an increase in MVO2, whereas isoflurane increases coronary flow by decreasing Do2 without decreasing MVO2. This indicates that isoflurane, a directly acting coronary artery vasodilator, accentuates the compensatory coronary vasodilatory effect of amrinone that results from increased MVO2.

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effect of amrinone on the basis of pressure-derived indices of contractility;\textsuperscript{13,14} one report\textsuperscript{13} has suggested that the reduction in peripheral resistance induced by amrinone results in a reflex increase in sympathetic tone via pressor receptors.

Volatile anesthetics are potent depressors of the cardiovascular system;\textsuperscript{15–22} they appear to have quantitatively different effects on many components in the sequence of excitation–contraction coupling.\textsuperscript{18–22,††} Makena and Kapur\textsuperscript{23–25} have demonstrated in the dog that amrinone is capable of blunting the cardiac depressant effect of enflurane and isoflurane.

No studies have been published on the direct and interactive effects of volatile anesthetics and amrinone on cardiac electrophysiology, contractile function, coronary flow, and myocardial $O_2$ uptake. One aim was to establish the dose-dependent effects of amrinone as a primary cardiotoxic agent. We investigated amrinone’s direct effects on increasing heart rate, contractility, and myocardial $O_2$ consumption ($MV_{O_2}$) and examined whether it has a direct coronary vasodilator effect. A second aim was to determine if amrinone can antagonize the known cardiodepressant effects of isoflurane and augment the coronary vasodilator effect of isoflurane. We chose the isolated heart model, in which extrinsic variables such as baroreceptor-induced reflexes and preload volume and afterload impedance are avoided, so that we could readily examine the direct effects of amrinone and isoflurane on spontaneous heart rate, atrioventricular conduction time (AVCT), coronary flow, $O_2$ delivery, $MV_{O_2}$, percent $O_2$ extraction, and the $O_2$ supply-to-demand ratio.

Materials and Methods

After approval from the Animal Studies Committee, 11 Albino short-haired guinea pigs (250–450 g) were injected with 10 mg ketamine and 1,000 U heparin and were decapitated when unresponsive to noxious stimulation. After thoracotomy, the inferior and superior vena cava were cut, and the aorta was cannulated distal to the aortic valve. Each heart was immediately perfused in a retrograde direction through the aorta and was excised. The venae cavae were ligated, and the right ventricle was cannulated through the pulmonary valve to collect coronary sinus effluent. The perfusate, a modified Krebs–Ringer’s solution, had the following composition (in mM):\textsuperscript{25}\textsuperscript{26,27} Na$^+$ 137, K$^+$ 5.9, Mg$^{2+}$ 1.2, Ca$^{2+}$ 2.0, Cl$^-$ 154, HCO$_3^-$ 15.5, $H_2$PO$_4^-$ 1.2, pyruvate 2, glucose 11.5, mannitol 16, and ethylenediaminetetraacetic acid 99% (EDTA) 0.05.

The solution was filtered (Astrodisc®, Gelman Sciences, Ann Arbor, MI) and equilibrated with a 96% $O_2$–4% CO$_2$ gas mixture delivered at 3 l/min. Mean aortic inflow $p_H$, CO$_2$ tension (P$_{CO_2}$), and $O_2$ tension (P$_{O_2}$), determined at the beginning and at the end of each exposure to control and treatment solutions with a blood-gas analyzer (Radiometer®ABL-2, Medtronic Chicago, Des Plaines, IL), were 7.41 ± 0.01, 35 ± 1, and 525 ± 5 mmHg (mean ± SEM), respectively. Hearts were perfused with a non-recirculating perfusate and were submerged in a bath of perfusate solution. Perfusion and bath temperature were maintained at 36.6 ± 0.15°C by means of a thermostatically controlled water circulating system (Haake E52®, Haake Buchlar Inc., Saddle Brook, NJ). The perfusion pressure was maintained at 55 mmHg with a 75-cm-high fluid column maintained with an overflow pump that returned excess solution to the reservoir. Perfusion pressure was measured at the aortic root with a pressure transducer.

Two pairs of bipolar electrodes (Teflon®-coated silver, diameter 125 μm; Cooner Wire, Chatworth, CA) were placed in each heart to monitor intracardiac electrograms from which spontaneous sinoatrial (SA) rate and conduction times were measured as reported previously. Sinus cycle length was measured and heart rate was calculated from the superior right atrial beat-to-beat interval; AVCT was determined from the superior right atrial to left ventricular septal beat-to-beat interval. The two electrode signals were amplified 100- or 1,000-fold; were filtered at frequencies below 1 Hz and above 10 kHz; and were displayed continuously on a polygraph (Astro-Med MT 9500R, Astro-Med, West Warwick, RI) and on an image-storing oscilloscope (5A26, 5113, Tektronix, Beaverton, OR). Electrogram intervals were measured automatically by digital timer systems that allowed instantaneous beat-to-beat interval and rate analyses.

LVP was measured with a transducer connected to a thin, saline-filled latex balloon (Hugo Sachs Electronic AG, Germany) inserted into the left ventricle through the mitral valve from a cut in the left atrium. The balloon volume was adjusted to maintain a diastolic pressure of zero to minimize end-diastolic wall stress, which can occur with higher resting balloon volumes. Coronary flow was measured with a 1.5-mm extracorporeal flow probe (Biotronix® BL610, Biotronix Laboratories, Kensington, MD) placed into the aortic inflow line. Zero flow was established periodically by temporarily bypassing the flow probe. The flow probe was calibrated by timed collections into a volumetric cylinder over the range of measured flow. Coronary inflow (a) and outflow (y) P$_{O_2}$ were measured continuously on-line (203B, Instech Laboratories, Plymouth Meeting, PA) and verified intermittently with an off-line continuously calibrating O$_2$ electrode (Radiometer® ABL-2). The in-line miniature Clark O$_2$ electrodes were cali-
brated with a bypass circuit with 100% N₂, 20% O₂, and 96% O₂ dissolved in Krebs–Ringer’s solution to adjust P O₂ to 20, 150, and 600 mmHg.

These variables were calculated: O₂ delivery (\(\text{DO}_2\)) = CF 
\(\times P_{O_2} \cdot O_2\) solubility, in microliters per gram per minute; 
\(\text{MV}_{O_2} = CF \times \left( P_{O_2} - P_{O_2}\right) \cdot O_2\) solubility, in microliters per gram per minute; and percent O₂ extraction = \(\left( P_{O_2} \right)/P_{O_2} \cdot 100\). O₂ solubility is 24 µl/ml H₂O at 760 mmHg. Electrograms, sinus cycle length, AVCT, LVP, aortic (coronary) perfusion pressure, coronary flow and in-line P O₂ were intermittently tape-recorded (D1, Vetter, Rebersburg, PA) for later detailed analysis.

Isoflurane was given to hearts by switching to oxygenated perfusate equilibrated with the vapor (isoflurane-specific vaporizer, Ohio Medical Products, Madison, WI). Vaporizer settings were 0.5 and 1.0 vol%, which correspond to approximately 0.5 and 1.0 minimum alveolar concentration (MAC) for isoflurane in humans and guinea pigs. The vaporizer settings were checked for accuracy by mass spectrometry at the delivered flow of 31/min. Perfusate was collected at an aortic inflow side port into sealed, air-free, 1-m1 vials for measurement of isoflurane concentrations by gas chromatography. Mean perfusate concentrations for 0.5 and 1.0 vol% were 110 ± 30 and 210 ± 36 µM, respectively. Amrinone (5-amino-[3,4-bipyridine]-6[1H]-one) lactate (Inocor®, Winthrop Pharmaceuticals, New York, NY), 5 mg/ml, was freshly diluted in perfusate and administered for 10-min periods at 10, 50, 100, and 500 µM concentrations. Control washout periods between perfusions of amrinone (data not shown) demonstrated a return of values to initial baseline concentration values. Perfusate concentrations and exposure periods were based on preliminary experiments for submaximal, steady-state cardiac effects. Adenosine (0.2 ml 200 µM stock) was injected at the beginning and at the end of each experiment to establish maximal coronary flow during arrested and paced (240 beats per min) conditions.

Protocol and Statistical Analyses

Drug-free control measurements were recorded after a 30-min stabilization period. No hearts had more than two single premature atrial or ventricular beats per minute in the initial control period or throughout the study period. Each heart was exposed, in random order, to amrinone alone and to amrinone with isoflurane, which was administered before, during, and after amrinone infusion. The order of concentrations of amrinone (10, 50, 100, and 500 µM) and of isoflurane (0.5 or 1.0%) were randomized. The four concentrations of amrinone were given with one and then the other concentration of isoflurane.

All values are means ± SEM. Data were analyzed by one-way analysis of variance; when F values were significant, means were compared by tests of least significant difference of means (software: Statview® Abacus Concepts, Calabasas, CA and CLR®, Clearlake Research, Houston, TX; Macintosh® SE30 computer, Apple Computer Inc., Cupertino, CA). For each variable the following were examined: 1) the effects of amrinone and isoflurane, singularly and together, versus initial (drug-free) controls, and 2) the effects of each level of isoflurane plus amrinone versus each level of isoflurane alone (isoflurane controls). To determine dose-dependent effects, linear regression analysis was used. The change in each variable from initial control values was analyzed as a function of isoflurane concentration (vertical data) or as a function of the log₁₀ concentration of amrinone (horizontal data). Probability (P) values <0.05 were considered statistically significant.

Results

Table 1 displays actual mean control values and experimental values obtained solely during combined treatment with 500 µM amrinone plus 1% isoflurane. Of the eight variables measured, only heart rate and LVP were similar to control values at the highest concentrations of amrinone and isoflurane. Postcontrol values were not significantly different from the initial control values. Figures 1–7 display in detail the responses to the four concentrations of amrinone and the two concentrations of isoflurane, administered alone or combined. Figure 1 shows the individual and combined effects of isoflurane and amrinone on the percentage change in spontaneous heart rate. Isoflurane alone (0.5% and 1.0%) decreased heart rate in a dose-dependent manner (\(P < 0.001\), by 4.7 ± 0.5% and by 7.8 ± 0.6%, respectively. Amrinone alone significantly increased heart rate, by 9.1 ± 0.6% at 500 µM, and attenuated the negative chronotrophic effect of isoflurane so that heart rate returned to the nontreated mean control value during treatment with 1% isoflurane and 500 µM amrinone. The heart rate effects of amrinone alone or with isoflurane were dose-dependent (\(P < 0.001\)).

Figure 2 shows that isoflurane alone caused significant, dose-dependent (\(P < 0.001\)) increases in AVCT (3.5 ± 0.3 and 4.6 ± 0.3 ms). Administration of amrinone alone caused significant, dose-dependent (\(P < 0.001\)) decreases in AVCT (−0.9 ± 0.2 to −2.8 ± 0.5 ms); amrinone plus isoflurane also produced dose-dependent decreases in AVCT. Amrinone (500 µM) completely counteracted the negative chronotropic effect of 0.5% isoflurane and partially reversed the effect of 1% isoflurane.

Isoflurane alone (\(P < 0.001\)) decreased contractile function (fig. 3) in a dose-dependent manner, as shown by the percentage decreases in isovolumetric LVP (−6.9 ± 0.4 and −13.2 ± 0.4%). Also in a dose-dependent manner, administration of amrinone alone or with isoflurane increased LVP (\(P < 0.001\)); the increase was 12.8 ± 0.9%
TABLE 1. Initial Control, Peak Dose, and Postcontrol Values

<table>
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<tr>
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<th>Control</th>
<th>500 μM AMR + 1% ISO</th>
<th>Postcontrol</th>
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<tbody>
<tr>
<td>Heart rate (beats per min)</td>
<td>216 ± 5</td>
<td>216 ± 4</td>
<td>217 ± 5</td>
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<td>AV conduction time (ms)</td>
<td>55.7 ± 0.6</td>
<td>57.4 ± 0.8*</td>
<td>55.7 ± 0.7</td>
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<td>LV pressure (mmHg)</td>
<td>86.4 ± 3.4</td>
<td>87.1 ± 1.6</td>
<td>85.2 ± 3.2</td>
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<td>Coronary flow</td>
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<tr>
<td>(ml·min⁻¹·g⁻¹)</td>
<td>6.3 ± 0.3</td>
<td>9.0 ± 0.5*</td>
<td>6.3 ± 0.4</td>
</tr>
<tr>
<td>D₀₂ (ml·min⁻¹·g⁻¹)</td>
<td>100.3 ± 2.6</td>
<td>141.1 ± 3.2*</td>
<td>107.5 ± 2.7</td>
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<tr>
<td>MV O₂ (ml·min⁻¹·g⁻¹)</td>
<td>55.8 ± 3.6</td>
<td>68.6 ± 3.4*</td>
<td>55.5 ± 3.7</td>
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<tr>
<td>O₂ extraction (%)</td>
<td>52.3 ± 2.2</td>
<td>44.6 ± 2.2*</td>
<td>52.4 ± 3.2</td>
</tr>
<tr>
<td>D₀₂/MV O₂ ratio</td>
<td>1.75 ± 0.08</td>
<td>2.06 ± 0.10*</td>
<td>1.76 ± 0.08</td>
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Data are means ± SEM; n = 11 hearts.
* P < 0.05 versus initial control. Postcontrol values after treatment with 500 μM amrinone (AMR) and 1% isoflurane (ISO) are not significantly different from initial control values.

with 500 μM amrinone alone. Amrinone, 100 and 500 μM, neutralized the negative inotropic effect of 0.5 and 1% isoflurane, respectively, whereas 500 μM amrinone plus 0.5% isoflurane caused a 2.8 ± 0.7% increase in LVP above the mean drug-free control value.

Figure 4 demonstrates that 1% isoflurane alone produced significant dose-dependent (P < 0.001) increases (10.1 ± 0.8 and 19.9 ± 0.7%) in coronary flow. Administration of amrinone alone or with isoflurane produced dose-dependent increases in coronary flow (P < 0.001); the increase was 18.3 ± 0.9% with 500 μM alone. Amrinone administered during exposure to isoflurane caused further additive increases in coronary flow; coronary flow increased to 42.4 ± 1.7% with 500 μM amrinone plus 1% isoflurane. The increase in coronary flow induced by this combination was significantly lower than were the increases during temporary arrest by adenosine (88 ± 3% initial control, 74% ± 3% postcontrol) or those during cardiac pacing at 240 beats per min (75 ± 4% initial control).

Isoflurane 0.5 and 1% alone caused no significant change (−1.7 ± 0.5 and −1.8 ± 0.6%) in MV O₂, whereas amrinone alone increased MV O₂ by 22.8 ± 3.8% at 500 μM (fig. 5). The increases in MV O₂ with amrinone alone or with isoflurane were dose-dependent (P < 0.001), and the changes in MV O₂ with 0.5 and 1% isoflurane plus amrinone were similar to those with amrinone alone. Figure 6 displays the percent changes in the fraction of O₂ extracted. Isoflurane 0.5 and 1.0% alone (P < 0.001) reduced percent O₂ extraction in a dose-dependent manner.

**Fig. 1.** Individual and combined effects of isoflurane and amrinone on heart rate as a percentage of initial drug-free control values. CTRL 1, CTRL 2 = initial and final drug-free control values, respectively. *Significance of amrinone (AMR) and isoflurane (ISO) singularly and together versus CTRL 1 (P < 0.05). †Significance of AMR plus ISO versus respective ISO level alone (P < 0.05). Values are means SEM; n = 11 hearts.

**Fig. 2.** Individual and combined effects of isoflurane and amrinone on the change in atrioventricular conduction time (AVCT) from initial drug-free control values. Notations are the same as in figure 1.
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AMRINONE (μM)

**FIG. 3.** Individual and combined effects of isoflurane and amrinone on left ventricular (LV) systolic pressure as a percentage of initial drug-free control values. Notations are the same as in figure 1.

**FIG. 5.** Individual and combined effects of isoflurane and amrinone on myocardial O₂ consumption as a percentage of initial drug-free control values. Notations are the same as in figure 1.

by 10.8 ± 0.6 and 18.0 ± 0.9%, respectively, whereas amrinone produced no significant change in the percent O₂ extracted (3.8 ± 2.3% at 500 μM); the changes in percent O₂ extracted with amrinone alone or with isoflurane were not dose-dependent. The percent change in the fraction of O₂ extracted with isoflurane plus amrinone was less than and parallel to that of amrinone alone. Figure 7 shows that the O₂ supply-to-demand ratio, which is inversely proportional to the percent O₂ extracted (P < 0.001), increased 11.1 ± 0.7 and 18.2 ± 0.9% with 0.5 and 1% isoflurane in a dose-dependent manner and was not affected by amrinone alone. The effects of amrinone alone or with isoflurane on this ratio were not dose-de-

**FIG. 4.** Individual and combined effects of isoflurane and amrinone on coronary blood flow as a percentage of initial drug-free control values. Notations are the same as in figure 1.

**FIG. 6.** Individual and combined effects of isoflurane and amrinone on percent myocardial O₂ extraction as a percentage of initial drug-free control values. Notations are the same as in figure 1.

Discussion

This study demonstrates that amrinone is a direct cardiac stimulant that is capable of overcoming the direct cardiac depressant effects of isoflurane at the concentrations used in this study. In summary, our findings for the isolated heart are as follows. 1) Amrinone produces a dose-dependent increase in spontaneous heart rate, and this increase can counteract the dose-related decrease in heart
rate produced by isoflurane. 2) Amrinone produces a dose-dependent increase in atrioventricular (AV) conduction time, which can counteract the dose-related negative dromotropic effect produced by isoflurane. 3) Amrinone produces a dose-dependent direct positive inotropic effect, as evidenced by a stepwise increase in isovolumetric LVP, which can counteract the myocardial depressant effect produced by isoflurane. 4) Amrinone increases coronary flow concomitant with an increase in $\text{MV}_2\text{O}_2$, while isoflurane increases coronary flow without causing a change in $\text{MV}_2\text{O}_2$. 5) Amrinone causes a stepwise increase in $\text{MV}_2\text{O}_2$, which is not changed in the presence of isoflurane. 6) Isoflurane causes a stepwise decrease in percent $\text{O}_2$ extraction, which can be increased only minimally by amrinone in the presence of isoflurane. 7) Isoflurane causes a stepwise increase in the $\text{O}_2$ supply-to-demand ratio, which can be decreased only minimally by amrinone in the presence of isoflurane. 8) The increase in this ratio with isoflurane plus amrinone results primarily from the excessive increase in $\text{O}_2$ delivery afforded by isoflurane, because the increase in $\text{O}_2$ delivery by amrinone only matched the increase in $\text{MV}_2\text{O}_2$.

FIG. 7. Individual and combined effects of isoflurane and amrinone on oxygen supply ($\text{DO}_2$) to myocardial $\text{O}_2$ consumption ($\text{MV}_2\text{O}_2$) ratio. Notations are the same as in figure 1.

**EFFECTS ON HEART RATE**

Although it is generally claimed that amrinone has a negligible effect on heart rate in *vivo*, the direct positive chronotropic effect that we noted confirms the findings of a number of other in *vivo* studies, e.g., those on the isolated guinea pig heart and on the isolated dog heart. The positive chronotropic effect can probably be explained similarly to the positive inotropic effect, i.e., by selective inhibition of PDE III. In *vivo*, an increase in the rate–pressure product and thus in the myocardial $\text{O}_2$ demand with excessive doses of amrinone could be deleterious if myocardial $\text{O}_2$ supply is lowered or if coronary reserve is limited. However, at lower concentrations amrinone does not appear to cause a significant increase in heart rate, such that the increase in $\text{MV}_2\text{O}_2$ is limited.

This report as well as others indicates that isoflurane has a direct dose-related negative chronotropic effect that is the result primarily of a reduced rate of increase of phase 4 and phase 0 of the action potential of the SA nodal cells, attenuation of the slow Ca$^{2+}$ channel influx rather than competitive antagonism of adrenergic receptors may underlie the mechanism. In this study, amrinone was capable of completely reversing the negative chronotropic effect of isoflurane.

**EFFECTS ON AV CONDUCTION TIME**

The AV node, as well as the SA node, depends largely on Ca$^{2+}$ influx for phase 4 and phase 0 depolarization. Therefore, it is to be expected that any drug-induced changes in Ca$^{2+}$ influx will alter AV conduction. Our data show that amrinone causes a direct dose-related decrease in AVCT. Enhanced AV conduction has previously been demonstrated with high doses of amrinone. This account for its ability to accelerate the ventricular response in atrial fibrillation. Amrinone has been shown to be less active in accelerating AV nodal conduction than in enhancing SA node automaticity. Although electrophysiologic studies suggest that amrinone does not have any significant proarythmic potential during acute administration, bigeminy and enhanced automaticity have been noted in an isolated rabbit papillary muscle exposed to high doses of amrinone, and amrinone has been shown to sensitize isolated canine ventricular tissue to the dysrhythmic effects of reperfusion. No dysrhythmic phenomena were noted in this study. The negative dromotropic effect of isoflurane is well established and can be explained at least partially by its Ca$^{2+}$ channel antagonism. The AV conduction slowing induced by isoflurane could be reversed completely by higher doses of amrinone.

**EFFECTS ON LVP**

This data demonstrate that amrinone moderately increases isovolumetric LVP in a dose-dependent manner; this indicates that in the *in vitro* heart, amrinone is indeed a positive inotropic drug. This is in contrast to the findings of a number of investigations in animals and hu.

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In which no evidence for a direct inotropic effect could be found. These investigators attributed the salutary effects of amrinone solely to its potent vasodilator property, which, by decreasing peripheral vascular resistance, reduces preload and afterload. However, other investigators, using various animal models, e.g., isolated cardiac muscle, 23,33 isolated guinea pig heart, 26 intact canine preparations, 23-25 and isolated dog heart preparations, 27,34,35 have been able to demonstrate that amrinone exerts a direct positive inotropic effect. Furthermore, a number of human clinical studies have indicated a positive inotropic effect. 1,2,5,10

Increased Ca\(^{2+}\) influx appears to be the major mediator of amrinone's ultimate physiologic actions. Amrinone inhibits PDE III, an enzyme responsible for the degradation of cAMP. 2-4 Increased intracellular cAMP results in activation of protein kinases that catalyze the transfer of phosphate groups from adenosine triphosphate to intracellular proteins; this in turn causes an increased number of slow Ca\(^{2+}\) channels in a favorable configuration for Ca\(^{2+}\) influx, as well as a potentiation of Ca\(^{2+}\) delivery to the contractile system. Amrinone has been reported to increase the slow inward Ca\(^{2+}\) current in voltage clamp preparations. 7,8 Experimental evidence suggests that amrinone also promotes intracellular Ca\(^{2+}\) accumulation by a mechanism that involves Na\(^{+}\)/Ca\(^{2+}\) exchange but is independent of PDE inhibition. 4 In addition, amrinone has been shown to alter the pattern of the rate of cardiac muscle relaxation and the ability of the sarcoplasmic reticulum to sequester and directly or indirectly to release Ca\(^{2+}\). 36

The dose-dependent myocardial depressant effects of isoflurane are consistent with those of other studies. 15,16,18-22, 18 Volatile anesthetics are known interfere with the slow Ca\(^{2+}\) current across the sarcolemma and have been shown to alter intracellular Ca\(^{2+}\) homeostasis. 14, 18 They cause a reduction in Ca\(^{2+}\) release from internal stores, which reduces the availability of Ca\(^{2+}\) to the contractile proteins. The inotropic effect of AMR has been shown to overcome the depressant effect of halothane in rabbit papillary muscle stimulated at 0.1-0.5 Hz 22 and of enflurane and isoflurane in an intact dog preparation. 23,24

In the current study, performed in isolated hearts, the higher concentrations of amrinone completely reversed the myocardial depressant effect of isoflurane. From evidence on the mechanism of action of these agents it is likely that amrinone and volatile anesthetics have opposing actions on intracellular Ca\(^{2+}\) mobilization.

Effects on Coronary Flow

Amrinone caused a dose-related increase in coronary flow, a result consistent with the findings of other in vitro 26,37,34,37,39 and in vivo 39,40 studies. Although this increase must be in part an autoregulatory phenomenon, secondary to an increase in LVP and MV\(_{O_2}\), it also may be a direct effect, for amrinone has been shown to dilate the systemic and pulmonary vascular beds. 9,11,14 The mechanism of peripheral vasodilation by amrinone is not known, but it possibly involves enhancement of endogenous adenosine, 12 inhibition of cAMP breakdown, or nonspecific attenuation of Ca\(^{2+}\) fluxes. 11 This study demonstrates that the cause for the increase in coronary flow with amrinone was different than that with isoflurane because amrinone did not increase coronary flow to a level greater than the metabolic requirement of the heart, whereas isoflurane did. This can be seen by the matched increases in O\(_2\) delivery and MV\(_{O_2}\) with amrinone and the increase in O\(_2\) delivery and absence of change in MV\(_{O_2}\) with isoflurane. This suggests that amrinone is not a direct coronary vasodilator in this model; instead the flow increase with amrinone accounts for the increase in metabolic requirements accompanying its direct positive chronotropic and inotropic effects. Its peripheral vasodilatory effects, as shown by others, 9,10 may be greater.

As also shown in other studies using this preparation, 29,32 isoflurane produces coronary vasodilation in excess of metabolic need, as seen by a larger increase in O\(_2\) delivery that was not accompanied by a significant change in MV\(_{O_2}\). However, the 20% increase in coronary flow with 1% isoflurane is well below the maximal flow obtained with adenosine even when hearts are paced. 22 This indicates that 1% isoflurane is a directly acting, moderately potent vasodilator. The coronary vasodilatory effect of isoflurane may be mediated, at least in part, by its Ca\(^{2+}\)-channel blocking effect. In combination with 500 \(\mu\)M amrinone, 1% isoflurane increased coronary flow 43% above control. Thus, the direct action of isoflurane and the compensatory action of amrinone produce additive coronary vasodilation.

Effects on MV\(_{O_2}\)

One aim of our study was to determine the extent to which amrinone has direct cardiostimulatory effects. Along with increases in heart rate and contractile function, amrinone caused a dose-related increase in MV\(_{O_2}\). It has been asserted that, in vivo, amrinone has no effect on or even decreases MV\(_{O_2}\). 9,10 The absence of an increase in MV\(_{O_2}\) with amrinone, particularly in patients with severe congestive heart failure, 8 can be explained best by its more prominent peripheral venous and arteriolar vasodilatory effect, which causes a decrease in afterload impedance and end-diastolic ventricular volume. This reduces left ventricular filling pressure and thereby reduces wall tension, which in turn lowers the myocardial O\(_2\) requirement. 8 It is possible that the increase in O\(_2\) demand generated by the positive inotropic action of amrinone is offset by the reduction in O\(_2\) demand that is caused by a
decrease in wall tension due to a decrease in ventricular dilatation. However, in the isolated heart preparation, this secondary decrease in wall tension obviously does not occur, and since the other two dynamic determinants of $\text{MV}_{\text{O}_2}$—heart rate and LVP—are increased, $\text{MV}_{\text{O}_2}$ also increases. Increases in $\text{MV}_{\text{O}_2}$ induced directly by amrinone have also been reported in other in vitro studies.  

Despite the decreases in heart rate and LVP effected by isoflurane, the decrease in $\text{MV}_{\text{O}_2}$ was only marginal and was not significant. This lack of a significant decrease in $\text{MV}_{\text{O}_2}$ with isoflurane may be due to increased coronary flow and $\text{O}_2$ delivery (Gregg’s phenomenon). As shown in the current and a previous study, isoflurane increases $\text{O}_2$ delivery more than it decreases $\text{MV}_{\text{O}_2}$. Amrinone, as might be expected, reverses this slight decrease in $\text{MV}_{\text{O}_2}$ due to isoflurane and increases $\text{MV}_{\text{O}_2}$ in a dose-dependent manner. The percent $\text{O}_2$ extracted did not increase significantly with amrinone; this indicates that the increase in $\text{O}_2$ demand, occasioned by the increase in LVP, was adequately compensated for by the increase in $\text{O}_2$ delivery resulting from the rise in coronary flow. $\text{O}_2$ extraction dropped significantly with administration of isoflurane, a result consistent with the decreased $\text{O}_2$ demand caused by a decrease in heart rate and LVP. Moreover, administration of amrinone only partially reversed the decrease in $\text{O}_2$ extraction due to isoflurane.

Our findings in the isolated guinea pig heart indicate that amrinone is indeed a direct cardiac stimulant that can compensate for the direct depressant effects of isoflurane. Amrinone probably lacks a direct coronary arteriolar vasodilatory effect: it produces an increase in coronary flow that only matches the increase in $\text{MV}_{\text{O}_2}$. Extrapolation of these results to patients treated with amrinone during isoflurane anesthesia is limited in that many other cardiac and extracardiac factors are involved in vivo. Measured plasma concentrations of amrinone after loading doses of 0.5–3.5 mg/kg in patients, followed by an infusion of $10–40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, are about $10–100 \mu\text{M}$. Protein binding is minimal. Thus, the lower peripheral concentrations used in this study are probably clinically relevant. Since amrinone, unlike catecholamines, does not act via $\beta_1$ receptors, it can help to achieve an improvement in cardiac function even in patients in whom maximal doses of catecholamines have failed due to $\beta_1$ receptor down-regulation. Patients with poor left ventricular function after cardiopulmonary bypass and patients with borderline left ventricular function who are undergoing noncardiac surgery may benefit from short-term use of amrinone perioperatively. Since both amrinone and isoflurane are peripheral vasodilatory agents, their combination may cause hypotension despite the cardiac stimulatory effects of amrinone.

References
18. Lynch C III: Differential depression of myocardial contractility


