Bipyridine Derivatives Lower Arteriolar Resistance and Improve Left Ventricular Function in Newborn Lambs

J. Y. COE, P. M. OLLEY, G. VELLA, AND F. COCEANI

Divisions of Cardiology and Neurosciences, Department of Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada

ABSTRACT. Milrinone may be used in the treatment of pulmonary hypertensive diseases of the newborn. We have studied its effects in chronically instrumented newborn lambs over a dose range from 1-100 $\mu\text{g/kg}$. These actions have been compared with those of amrinone. We have also tested the effect of milrinone on hypoxia and leukotriene D_4 -induced pulmonary vasoconstriction. Injected into the right pulmonary artery, both amrinone and milrinone cause a dose-related fall in pulmonary arteriolar resistance with milrinone being approximately 20 times more potent than amrinone and possessing an ED_{50} of about 10 $\mu\text{g/kg}$. Both agents increase left ventricular dp/dt significantly and tend to increase cardiac output. Systemic vascular resistance falls with both drugs but the change is significant only with milrinone. While milrinone attenuates the increase in pulmonary arteriolar resistance induced by leukotriene D_4 and hypoxia, this is probably an indirect effect. Milrinone does not modify either the increases in left atrial, aortic pressure, and systemic vascular resistance or the decreases in cardiac output and left ventricular dp/dt induced by leukotriene D_4 . These findings suggest that milrinone deserves clinical trial in newborn infants with pulmonary hypertension in whom myocardial depression often coexists. (*Pediatr Res* 22: 422-428, 1987)

Abbreviations

PE, polyethylene
HPLC, high performance liquid chromatography
ANOVA, analysis of variance
Qinj, flow in injected lung
Qt, pulmonary blood flow

Persistent pulmonary hypertension of the newborn describes a syndrome in which increased pulmonary vascular resistance is associated with right-to-left shunting through the foramen ovale and the ductus arteriosus. It excludes pulmonary hypertension secondary to cardiac malformations.

Possible etiologic factors include perinatal hypoxemia, fetal hypertension, *in utero* constriction of the ductus arteriosus either spontaneous or secondary to maternal ingestion of nonsteroidal antiinflammatory agents, lithium intoxication, and neonatal polycythemia.

Impaired coronary perfusion and systemic hypoxemia often depress myocardial function in these patients, thereby adding to the therapeutic problem. Indeed, severe forms of this syndrome carry a 25 to 30% mortality (1, 2).

Because active pulmonary vasoconstriction is believed to be a significant factor in the pathogenesis of persistent pulmonary hypertension, many vasodilators have been tried with inconsistent effects. With most such drugs systemic vasodilation with hypotension limits their usefulness.

The bipyridine derivatives, amrinone [WIN 40680, 5-amino-3, 4'-bipyridine-6(1H)-one] and milrinone [WIN 47203, 1,6-dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carbonitrile] are positive inotropic agents in animals (3) and humans (4, 5) and smooth muscle relaxants. Amrinone has been the subject of a limited trial in children with pulmonary hypertension. In neonates it was possibly harmful, while in older children its benefits were limited by the rapid onset of tachyphylaxis (6). We have therefore studied the pulmonary vascular, cardiac, and systemic effects of milrinone in conscious, chronically instrumented young lambs and its effect on pulmonary vasoconstriction due to hypoxia, leukotriene D_4 , or both. Amrinone was also studied in one group of animals to provide comparative data. Milrinone differs from amrinone in being stable to light, it does not exhibit tachyphylaxis in adults (7) and causes fewer side-effects. It may therefore be a useful drug in pulmonary hypertensive diseases of the newborn.

MATERIALS AND METHODS

Twelve lambs of the Rambouillet breed, age 0.5-4 days (mean 1.7 days), weighing 3.6-5.8 kg (mean 4.7) were used in this study.

Surgical procedure. Under general anesthesia, a left thoracotomy was performed and two modified C & C Instruments electromagnetic flow probes were implanted, one around the right pulmonary artery and the other around the left pulmonary artery. Access to the right pulmonary artery was gained after ligating and dividing the ductus arteriosus. A special cannula through which a 41 cm, 3.5 French umbilical catheter (Argyle) could be passed was chronically implanted in the left atrium and secured by a purse string (8). The cannula was made from PE tubing (PE 205, OD 2.08 mm and ID 1.57 mm). A second smaller PE cannula (PE 90, OD 1.27 mm and ID 0.8 mm) was used to cannulate the right lower pulmonary vein.

At least 3 days were allowed for recovery from surgery. Any animal with evidence of respiratory distress was not used for subsequent drug studies.

Gentamicin (2 mg/kg) and ampicillin (125 mg) were administered intramuscularly postoperatively and twice daily thereafter.

Experimental procedure. The day before the drug study, a cutdown in the neck was performed under inhalation anaesthesia

Received May 13, 1985; accepted May 8, 1987.

Correspondence reprint requests Dr. Peter M. Olley, Department of Pediatrics, Room 2C300, Walter Mackenzie Health Sciences Centre, University of Alberta, Edmonton, Alberta, Canada T6G 2R7.

Supported by the Canadian and Ontario Heart Foundations

Amrinone and milrinone generously provided by Sterling Winthrop Ltd.

(halothane 0.5%, nitrous oxide 5 liter/min, oxygen 5 liter/min), which allowed the chronic placement of three vascular cannulae (Cook's Desilet-Hoffman Sheath Set) into a carotid artery (8 French) and both external jugular veins (7 French). Through these cannula, three additional catheters were introduced, one in the right atrium, a second in the right pulmonary artery with its tip just beyond the flow probe, and the third, a 5 French Millar high fidelity catheter, in the left ventricle. A Cook's Check-flow with a side connector was connected to the 8 French arterial cannula through which the high-fidelity catheter was passed. This arrangement allowed simultaneous arterial blood sampling and pressure monitoring through the side connection.

The fluid-filled catheters were connected to Statham P23dB strain gauge transducers, the flow probes to Statham SP2202 flow meters, and the Millar high fidelity catheter to a Millar Transducer Control Unit (model TCB 100). All signals (right and left pulmonary arterial flow, pulmonary, aortic, right and left atrial, pulmonary venous and left ventricular pressures, and left ventricular dp/dt) were displayed and continuously recorded on an Electronics for Medicine DR-8 optical recorder. Zero pressure was taken at midchest position. Three drugs were used in the experiments: amrinone alone (group 1), milrinone alone (group 2), leukotriene D₄ before and after treatment with milrinone (group 3). On each study day, only one test condition was used. Five animals were used in each group.

Dose responses to amrinone (100, 200, 500, and 1000 $\mu\text{g/kg}$) and milrinone (1, 10, 50, and 100 $\mu\text{g/kg}$) were obtained by using bolus injections into the right pulmonary artery. Thirty min were allowed to elapse between injections. The same sequence of dosage from low to high was used in all experiments. Flows and pressures were recorded continuously for the first 10 min after the injection and then at 5-min intervals thereafter. In two animals in group 1 and all animals in group 2, a control hypoxic pulmonary vasoconstrictor response was elicited before the drug test. In all animals in groups 1 and 2, the hypoxic response was again elicited 30 min after the last dose of amrinone or milrinone.

In group 3, bolus injections of leukotriene D₄ (1 $\mu\text{g/kg}$) and milrinone (50 $\mu\text{g/kg}$) were given into the right pulmonary artery. Ten min were allowed to elapse between the injections, during which the pressures and flows were monitored continuously. The test sequence was as follows: control bolus injections of leukotriene D₄ were made in room air and the hemodynamic effects measured. After return to baseline, hypoxia was induced. A second bolus injection of leukotriene D₄ was made during sustained hypoxia. The animals were then returned to room air,

and milrinone 50 $\mu\text{g/kg}$ was administered after the hemodynamic parameters had returned to baseline normoxic levels. Ten min after this, bolus injections of leukotriene D₄ were repeated during room air breathing and during sustained hypoxia.

During the study, the lamb was lightly restrained in a wooden frame. Normocapnic hypoxia was achieved by placing the animal in a plexiglass box through which a mixture of nitrogen, oxygen, and carbon dioxide was circulated to achieve a FiO_2 of 0.10–0.12. The hypoxic mixture was monitored continuously with a Critikon Oxycheck oxygen meter.

DRUGS AND SOLUTIONS

Amrinone was supplied in 1-ml ampoules containing amrinone as lactate equivalent to 5 mg and 0.25 mg sodium metabisulfite. Great care was taken in preventing its exposure to light. Milrinone powder was dissolved in 0.5 N lactic acid (2 mg/ml) and this stock solution was diluted with saline to the desired concentration.

An aqueous solution of synthetic leukotriene D₄ 1 mg/ml (courtesy of Dr. J. Rokach, Merck Frosst) was diluted with ice-cold Tris buffer (150 mM, pH 7.4).

Milrinone determination. Two ml of blood were withdrawn from the aorta into oxalated tubes 30 s after injection of milrinone and the plasma was separated and frozen. Plasma levels of milrinone were subsequently measured using the method of Edelson *et al.* (9) and a Waters 840 HPLC system.

The results are expressed as means $\pm$ SEM and analyzed by Student's *t* test (paired or unpaired) or ANOVA. Significance is regarded as a *p* value of less than 0.05. When a significant *F* value was obtained, the means were compared using Duncan's multiple range test. The surgical and experimental procedures were approved by the Animal Care Committee of the Research Institute, The Hospital for Sick Children, Toronto.

RESULTS

Group 1. Amrinone caused a dose-related fall in pulmonary arteriolar resistance in the injected lung (Fig. 1). The hemodynamic effect of the 1000 $\mu\text{g/kg}$ dose are shown in Figure 2. Left ventricular dp/dt increased significantly ($p < 0.05$). Systemic vascular resistance tended to fall in a dose-dependent fashion although the fall did not achieve significance. Intrapulmonary amrinone produced a redistribution of pulmonary blood flow toward the injected lung indicating a direct vasodilator effect.

Fig. 1. Percent change in pulmonary arteriolar resistance (PAR) in the injected lung in response to amrinone. Asterisk indicates significantly different from baseline in all legends ($p < 0.05$).

Fig. 2. Effects of 1000 $\mu\text{g/kg}$ of amrinone injected into the right pulmonary artery on systemic vascular resistance (SVR) $\blacktriangle$ — $\blacktriangle$; heart rate (HR) $\bullet$ — $\bullet$; pulmonary artery pressure (PAP) $\circ$ — $\circ$; left ventricular (LV) dp/dt, $\blacksquare$ — $\blacksquare$; cardiac index (CI) $\square$ — $\square$; and pulmonary arteriolar resistance (PAR) $\triangle$ — $\triangle$. The same abbreviations are used in subsequent figures.

Table 1. Effects of pulmonary artery injections on ratio of Q_{inj} to total Q_t *

% change in Q_{inj}/Q_t	Time (s)				
	10	20	30	60	120
Group I					
Amrinone (1000 $\mu\text{g/kg}$)	3.0† ±0.9	4.1† ±0.7	1.4† ±0.5	0.5 ±0.5	0.2 ±0.2
Group II					
Milrinone (50 $\mu\text{g/kg}$)	3.4† ±0.8	6.2† ±1.3	4.4† ±1.1	2.8† ±1.3	1.8 ±0.7
Group III					
Normoxia	-9.2†	-8.6†	-6.4	-3.3	-0.5
a) Leukotriene D_4	±2.2	±2.6	±2.2	±2.3	±0.5
b) Leukotriene D_4 + milrinone	-5.2	-12.1†	-8.2†	-4.8	-3.3
	±1.7	±2.6	±1.9	±2.2	±1.4
Hypoxia	-9.5†	-13.3†	-4.3	-4.2	-0.6
a) Leukotriene D_4	±2.2	±2.8	±2.4	±2.3	±0.6
b) Leukotriene D_4 + milrinone	-10.0†	-8.3†	-5.9	-2.2	-0.6
	±2.4	±1.5	±1.9	±1.1	±0.7

* Percentage change in ratio of Q_{inj} to total Q_t . A positive change indicates a direct dilator effect (amrinone, milrinone), a negative change suggests a constrictor action (leukotriene D_4). Leukotriene D_4 -induced changes in Q_{inj}/Q_t in normoxia or hypoxia was not altered by milrinone.

† Significant change $p < 0.05$.

The percent change in the ratio of Q_{inj} to total Q_t was significant for the highest dose with a shift toward the injected lung (Table 1).

Group 2. The vehicle (1.5 ml) had no effect on any of the hemodynamic parameters measured. As with amrinone, milrinone caused a dose-related fall in pulmonary arteriolar resistance (Fig. 3) and a dose-related increase in the ratio Q_{inj}/Q_t (Table 1). The effects of 50 and 100 $\mu\text{g/kg}$ of milrinone were comparable to that of 1000 $\mu\text{g/kg}$ of amrinone (Figs. 1 and 3). The ED_{50} for these actions was about 10 $\mu\text{g/kg}$.

Pulmonary artery pressure fell while cardiac output increased slightly (Fig. 4). Milrinone also caused a significant fall in systemic resistance (Fig. 5).

Bolus injections of 50 $\mu\text{g/kg}$ of milrinone increased the heart rate by 28 beats/min, and left ventricular dp/dt by 1980 mm Hg/s or 59% ($p < 0.01$). This rise in left ventricular dp/dt is

more than can be accounted for by the concomitant tachycardia (10).

Group 3. Leukotriene D_4 (1 $\mu\text{g/kg}$) caused pulmonary arteriolar constriction. This response was significantly attenuated by pretreatment with milrinone 50 $\mu\text{g/kg}$ (Fig. 6). Leukotriene D_4 also caused significant increases in left atrial pressure, aortic pressure, and systemic vascular resistance while decreasing cardiac output and left ventricular dp/dt (Fig. 7) and the flow ratio Q_{inj}/Q_t (Table 1). None of these changes was modified significantly by milrinone pretreatment.

Hypoxia. Hypoxia was used to induce heightened pulmonary vascular tone. Arterial blood gases were not significantly different between any of the groups before hypoxia and PO_2 fell to a similar degree (Table 2). Both amrinone and milrinone lowered the increase in pulmonary artery pressure and pulmonary arteriolar resistance induced by hypoxia. Similarly milrinone attenuated the response to leukotriene D_4 during both normoxia and hypoxia. The differences between control response and after treatment response were significant in all cases (Table 2).

Plasma levels. Plasma concentrations of milrinone increased with increasing dosage, and up to the 50 $\mu\text{g/kg}$ dose were inversely related to the fall in pulmonary arteriolar resistance in the injected lung (Fig. 8). There was no difference between the fall in pulmonary arteriolar and systemic resistances in response to 50 $\mu\text{g/kg}$.

DISCUSSION

Amrinone and its 2-methyl, 5-carbonitrile derivative milrinone are new agents with positive inotropic actions which are undergoing trials in the treatment of adults with congestive heart failure. They also relax vascular smooth muscle, including human umbilical arteries (11) and bovine intrapulmonary arteries (12). This action is not significantly affected by histamine H_1 and H_2 receptor blockers, cholinergic and adrenergic blockers, prostaglandin synthetase inhibitors, and is independent of muscarinic receptors. Evidence is accumulating that the bipyridines may relax vascular smooth muscle by affecting both calcium influx and its intracellular release. However, their mechanism of action is far from clear.

In isolated rat lungs amrinone dilates the pulmonary vessels and blunts hypoxic vasoconstriction (13). Mammel *et al.* (14) using a similar experimental model to ours showed that amrinone is a pulmonary vasodilator. Subsequent clinical studies were

Fig. 3. Percent change in PAR in the injected lung in response to milrinone.

Fig. 4. Effects of milrinone 50 µg/kg on PAP, LV dp/dt, PAR, HR, and CI.

Fig. 5. Effects of vehicle and graded doses of milrinone on SVR.

Fig. 6. Effects of leukotriene D₄ (LTD₄), 1 µg/kg, before and 10 min after milrinone (50 µg/kg) on PAR, PAP, left atrial pressure (LAP). Asterisk significantly different from baseline. The values for PAR at 20 and 30 s are significantly different ($p < 0.05$).

Fig. 7. Systemic and cardiac effects of leukotriene D₄, 1 µg/kg, before and 10 min after milrinone 50 µg/kg. AOP, aortic pressure; RAP, right atrial pressure.

Table 2. Effects of amrinone and milrinone on response to hypoxia and leukotriene D₄*

		Arterial blood gases		Response to hypoxia		
		Room air	Hypoxia	ΔPAP (mm/Hg)	ΔPAR (U/kg)	
Group 1	Control	PO ₂	70 (2)	46 (2)	6.7 ± 1.2	97 ± 19
		PCO ₂				
		pH				
	Amrinone	PO ₂	63.0 ± 0.5	43.2 ± 1.1	1.6 ± 1.2	25 ± 16
		PCO ₂	32.4 ± 1.2	36.6 ± 3.7		
		pH	7.47 ± 0.02	7.4 ± 1.3		
Group 2	Control	PO ₂	72.6 ± 2.6	44.0 ± 2.0	7.0 ± 1.5	100 ± 22
		PCO ₂	34.2 ± 1.3	34.4 ± 2.1		
		pH	7.47 ± 0.02	7.44 ± 0.02		
	Milrinone	PO ₂	80.0 ± 5.7	45.5 ± 1.7	2.2 ± 0.7	25 ± 11
		PCO ₂	33.4 ± 1.2	34.6 ± 0.7		
		pH	7.41 ± 0.02	7.44 ± 0.02		
		Arterial blood gases		Response to LTD ₄		
		Room Air	Hypoxia	ΔPAP	ΔPAR	
Group 3	Control	PO ₂	68.2 ± 2.6		29 ± 3	491 ± 96
		PCO ₂	33.4 ± 1.0			
		pH	7.43 ± 0.1			
	Milrinone	PO ₂	82.3 ± 9.0		21 ± 2	274 ± 75
		PCO ₂	34.5 ± 1.1			
		pH	7.46 ± 0.2			
Control	PO ₂		46.7 ± 0.9	20 ± 2	381 ± 97	
	PCO ₂		37.4 ± 1.2			
	pH		7.41 ± 0.01			
Milrinone	PO ₂		47.6 ± 0.4	17 ± 1	222 ± 42	
	PCO ₂		34.6 ± 1.1			
	pH		7.44 ± 0.01			

* Arterial blood gases in room air and during hypoxia before (control) and after pretreatment with either amrinone or milrinone. ΔPAP = increase in pulmonary artery pressure. ΔPAR = increase in pulmonary arteriolar resistance in response to hypoxia (groups 1 and 2) and to leukotriene D₄ 1 µg/kg in group 3. Leukotriene D₄ was tested in room air and hypoxia, before and after milrinone 50 µg/kg. All differences between control and treatment values for ΔPAP and ΔPAR are significant ($p < 0.05$). Group 1, unpaired data, groups 2 and 3, paired data ($n = 5$ for all observations except group 1 control PO₂ in which there were only two measurements). PO₂ and PCO₂ in mm Hg.

Fig. 8. Percent of maximum change in PAR plotted against plasma milrinone concentration 30 s after injection.

disappointing (6). In four neonates, 12–36 h old, intravenous amrinone lowered systemic pressure and arterial PO_2 with an apparent increase in cyanosis. In five older children with pulmonary hypertension, the initial dose of amrinone markedly decreased pulmonary artery pressure but in three of the five subsequent doses had little effect. Furthermore, frequent and potentially serious side-effects have been observed in adults including abdominal pain, nausea and vomiting, liver damage, myositis, pulmonary infiltrates, and polyserositis (15, 17). Thrombocytopenia without complication has also been reported (18).

Tachyphylaxis has not been reported with milrinone during its use in adults and over the short term it appears to be well tolerated without fever, thrombocytopenia, or gastrointestinal effects (7). Milrinone has the further advantage of being stable on exposure to light. The pulmonary vascular effects of milrinone have not been reported previously. Our studies show that it has significant relaxant action on pulmonary arterioles in young animals ($ED_{50} \sim 10 \mu\text{g/kg}$) that is approximately 20 times more potent than amrinone. This action is coupled with the expected positive inotropic action on the heart and systemic vasodilation.

Leukotrienes have been implicated as the mediator of hypoxic pulmonary vasoconstriction (19) and possible in the control of pulmonary blood flow in the fetus (20). We have previously demonstrated leukotriene D_4 to be a potent pulmonary vasoconstrictor in both lambs and piglets (21, 22) with negative inotropic properties (22). Our results suggest that milrinone blunts both hypoxia and leukotriene-induced pulmonary arteriolar constriction without significant effect on the leukotriene systemic action or on its negative inotropic effect. However, this apparent blunting is not reflected in the effect on the ratio Q_{in}/Q_t which suggests it may be an indirect action. The antagonistic action of milrinone on leukotriene effects is probably nonspecific but may be exerted through the common influence of these compounds on calcium fluxes (23).

The inotropic properties of amrinone have been demonstrated in isolated tissues (24) and humans (25). In anesthetized dogs bolus injections of amrinone increased flow to the left ventricle but the ratio of endocardial-to-epicardial perfusion fell, an effect that might encourage subendocardial ischemic damage in pathologic situations (26). The present study documents a direct positive inotropic action of milrinone in young lambs as judged by an increase in left ventricular dp/dt after its administration, which is greater than can be accounted for by the associated tachycardia (10). The concomitant fall in systemic resistance seen in our animals would be expected to reduce peak left ventricular dp/dt (27).

Pulmonary hypertension in the newborn is usually associated with right-to-left shunts through the foramen ovale and ductus arteriosus, factors that are often combined with myocardial depression. The "ideal" drug in these circumstances would be one in which completely selective pulmonary vasodilatation is coupled to a positive inotropic action on the heart. Effects on systemic resistance should be minimal. While milrinone is not ideal, our findings suggest that it is worth a trial in the management of these difficult clinical problems. It is a more potent pulmonary vasodilator than amrinone, it is a positive inotrope and, at high doses the fall in systemic resistance is much less than the fall in pulmonary resistance. There is some evidence that tachyphylaxis and side-effects are less of a problem with milrinone than amrinone, although the dose response relationship in our experiments suggests tachyphylaxis may be occurring. This will require further evaluation in the clinical setting.

Acknowledgments. The authors acknowledge the expert technical assistance of Mr. F. Hamilton, Mr. T. VanHelder, and Ms. R. Soni. Milrinone and amrinone were kindly provided by Dr. K. Nguyen of Sterling Drug Ltd. and Ltd₄ by Dr. J. Rokach of Merck Frost Canada Ltd.

REFERENCES

- Gersony WM 1979 Persistence of fetal circulation In: Godman MJ, Marquis RM (eds) *Pediatric Cardiology*, Vol 2. Churchill Livingstone, Edinburgh, pp 79–86
- Levin DL 1979 Primary pulmonary hypoplasia. *J Pediatr* 95:550–551
- Farah AG and Alousi AA 1978 New cardiotonic agents: a search for digitalis substitute. *Life Sci* 22:1139–1148
- Bain DS, McDowell AV, Cherniles J, Monrad ES, Parker JA, Edelson J, Braunwald E, Grossman W 1983 Evaluation of a new bipyridine inotropic agent—Milrinone—in patients with severe congestive heart failure. *N Engl J Med* 309:748–756
- Benotti JR, Grossman W, Braunwald E, Carabello BA 1980 Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive failure due to coronary artery disease. *Circulation* 62:28–34
- Kulik TJ, Johnson DE, Green TP, Locke JE 1984 Amrinone for pulmonary hypertension in infants and children. *Pediatr Res* 18:125A
- Timmins AD, Smyth P, Monaghan M, Atkinson L, Jewitt E 1984 Inotropic support with Milrinone in congestive heart failure. *Br Heart J* 51:691P
- Coe J, Olley PM, Hamilton F, VanHelder T, Coceani F 1987 A method to study pulmonary vascular response in the conscious newborn piglet. *Can J Physiol Pharmacol* 65:785–790
- Edelson J, Koss RF, Park JB 1983 High performance liquid chromatographic analysis of milrinone in plasma and urine. *J Chromatogr* 276:456–462
- Fisher DJ, Gross DM 1983 The effect of atrial pacing induced tachycardia on left ventricular contractile function in conscious newborn and adult sheep. *Pediatr Res* 17:651–656
- Wilmhurst PJ, Walker JM, Ivy CH, Mounsey JP, Twort CHC, Williams BT, Davies MJ, Webb-Peploe MM 1984 Inotropic and vasodilator effects of amrinone on isolated human tissue. *Cardiovasc Res* 18:302–309
- Harbison RG, Lipton HL, Hyman AL, Kadowitz PJ 1984 Pulmonary vascular

- actions of amrinone and milrinone. *Circulation* 70 (suppl II):182
13. Hill NS, Rounds S 1982 Amrinone is a pulmonary vasodilator and blunts hypoxic pulmonary vasoconstriction. *Am Rev Respir Dis* 125:270
 14. Mammel MC, Einzig S, Kulik T, Thompson TR, Lock JE 1983 Pulmonary vascular effects of amrinone in conscious lambs. *Pediatr Res* 17:720-724
 15. Jennings K, Gwilt P, Green P, Turnbull S, Gold R, Julian DG 1982 The clinical cardiovascular pharmacology of amrinone, a selective cardiotonic. *Acta Cardiol [Suppl] (Brux)* 28:67-75
 16. Likoff MJ, Weber KT, Andrews V, Janicki JS 1983 Amrinone: a promising new cardiotonic agent in the treatment of chronic cardiac failure. *Herz* 8:199-205
 17. Wilmhurst PT, Thompson DS, Juul SM, Jenkins BS, Coltart DJ, Webb-Peploe MM 1984 Comparison of the effects of amrinone and sodium nitroprusside on haemodynamics, contractility, and myocardial metabolism in patients with cardiac failure due to coronary artery disease and dilated cardiomyopathy. *Br Heart J* 52:38-48
 18. Ansell J, Tiarks C, McCue J, Parrilla N, Benotti JR 1984 Amrinone-induced thrombocytopenia. *Arch Intern Med* 144:949-952
 19. Ahmed T, Oliver W 1983 Does slow-reacting substance of anaphylaxis mediate hypoxic pulmonary vasoconstriction? *Am Rev Respir Dis* 127:566-571
 20. Soifer SJ, Loitz R, Roman C, Heyman M 1984 Do leukotriene (LT) control pulmonary blood flow (PBF) in fetal sheep? *Pediatr Res* 18:347A
 21. Yokochi K, Olley PM, Sideris E, Hamilton F, Huhtanen D, Coceani F 1982 Leukotriene D₄ a potent vasoconstrictor of the pulmonary and systemic circulations in the newborn lamb. In: Samuelsson B, Paoletti R (eds) *Leukotrienes and Other Lipooxygenase Products*. Raven Press, New York, pp 211-214
 22. Coe J, Hamilton F, Soni R, Hamilton F, Soni R, Coceani F, Olley P 1984 The effect of leukotrienes D₄ (LTD₄) on pulmonary arterioles, veins and left ventricular function in the conscious newborn piglet. *Circulation* 70 (suppl II):428
 23. Hattori Y, Levi R 1984 Leukotrienes C₄ and D₄ inhibit calcium-dependent contractility in potassium-depolarised guinea pig papillary muscle. *Fed Proc* 43:932
 24. Endoh M, Yamashita S, Taira N 1982 Positive inotropic effect of Amrinone in relation to cyclic nucleotide metabolism in the canine ventricular muscle. *J Pharmacol Exp Ther* 221:775-783
 25. deGuzman NT, Munoz O, Palmer RF, Davolos D, Alousi A 1978 Clinical evaluation of amrinone (A)—a new inotropic agent. *Circulation Res* 58(suppl 2):II-183
 26. Einzig S, Rao GHR, Pierpont ME, White JG 1982 Acute effects of amrinone on regional myocardial systemic blood flow distribution in the dog. *Can J Physiol Pharmacol* 60:811-818
 27. Barnes GE, Horowitz LD, Bishop VS 1979 Reliability of the maximum derivatives of left ventricular pressure and internal diameter as indices of the inotropic state of depressed myocardium. *Cardiovasc Res* 13:652-662