Anesthesiology
78:1166–1174, 1993

Amrinone and the Pulmonary Vascular Pressure–Flow Relationship in Conscious Control Dogs and Following Left Lung Autotransplantation

Daniel P. Nyhan, M.D., Charles G. Pribble, M.D.,† William P. Peterson, M.D.,‡ Kimitoshi Nishiwaki, M.D.,§ Gregory A. Trempy, M.D.,† Pankaj M. Desai, M.D.,† Peter Rock, M.D.,* Paul A. Murray, Ph.D.**

Background: **Amrinone, a bipyridine compound, is known to improve left ventricular function *via* its positive inotropic and afterload-reducing effects. The goal of this study was to assess the efficacy of amrinone as a pulmonary vasodilator, an effect that could be beneficial in the setting of right heart failure associated with pulmonary hypertension.**

Methods: **Investigated were the effects of intravenous amrinone (750 $\mu g/kg$ loading dose plus 1–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintenance dose) on the left pulmonary vascular pressure-flow ($LP\dot{Q}$) relationship in chronically instrumented, conscious dogs. The effects of amrinone on the $LP\dot{Q}$ relationship were assessed in a series of conscious control dogs with (n = 10) and without (n = 9) acute preconstriction with the thromboxane analog U46619 and in a series of conscious dogs 2–4 weeks after left lung autotransplantation (LLA) with (n = 8) and without (n = 8) acute U46619 preconstriction. Left pulmonary vascular pressure-flow plots were generated by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure/left atrial pressure [PAP/LAP]) and left pulmonary blood flow during gradual (~1 min) inflation of a hydraulic occluder implanted around the right pulmonary artery.**

Results: **Amrinone had no effect on the baseline $LP\dot{Q}$ relationship in control dogs. U46619 caused acute pulmonary vasoconstriction. For example, PAP/LAP at left pulmonary blood flow of 70 $ml \cdot min^{-1} \cdot kg^{-1}$ was increased ($P < 0.01$) from 16 ± 2 to 37 ± 2 mmHg during U46619 administration. In this setting of acute preconstriction, amrinone caused pulmonary vasodilation, *i.e.*, PAP/LAP was decreased ($P < 0.05$) from 37 ± 2 to 32 ± 2 mmHg. Left lung autotransplantation was associated with a marked shift in the $LP\dot{Q}$ relationship, indicating a chronic increase in pulmonary vascular resistance, *i.e.*, PAP/LAP was increased ($P < 0.01$) from 15 ± 2 to 32 ± 3 mmHg. Despite the chronic increase in pulmonary vascular resistance after LLA, amrinone had no effect on the baseline $LP\dot{Q}$ relationship. However, after acute preconstriction with U46619 after LLA, amrinone caused pulmonary vasodilation, *i.e.*, PAP/LAP was decreased ($P < 0.05$) from 45 ± 4 to 39 ± 4 mmHg.**

Conclusions: **These results indicate that amrinone exerts a significant, although relatively modest pulmonary vasodilator influence in the setting of acute pulmonary vasoconstriction in conscious control dogs and in conscious dogs after LLA. However, amrinone did not reverse the chronic increase in pulmonary vascular resistance associated with LLA. (Key words: Amrinone. Bipyridine compounds. Chronic instrumentation. Lung transplantation. Pulmonary circulation. Pulmonary hypertension. U46619.)**

THE bipyridines are nonglycosidic, noncatecholamine compounds used in the treatment of congestive heart failure. Amrinone, the most widely studied of these agents, selectively inhibits type III phosphodiesterase[1] and augments left ventricular function because of its positive inotropic and afterload-reducing effects.[2] A pulmonary vasodilator influence of amrinone would be beneficial, because it might attenuate pulmonary congestion and right ventricular failure in patients with either primary or secondary pulmonary hypertension. There is evidence to suggest that amrinone can decrease right ventricular afterload in the settings of cardiac failure[3,4] and critical mitral stenosis with pulmonary hypertension.[5] Amrinone also has been shown to decrease pulmonary vascular resistance (PVR) by ~50% in patients awaiting heart transplantation.[6] Only a relatively small number of laboratory investigations specifically assessed the pulmonary vascular effects of amrinone.[7–10] In studies using experimental models with a high degree of intrinsic pulmonary vasomotor tone, the bolus administration of amrinone resulted in a 20–

* Associate Professor.

† Assistant.

‡ Instructor.

§ Research Fellow.

Received from the Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland. Accepted for publication February 17, 1993. Supported by National Heart, Lung and Blood Institute grants HL-40361 and HL-38291 and a grant from Sterling-Winthrop Pharmaceuticals. Dr. Nyhan was supported as a Clinician Scientist by grant HL-02426. Presented at the annual meeting of the American Society of Anesthesiologists, October 26–November 1, 1991.

Address reprint requests to Dr. Murray: Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, 600 North Wolfe Street, Blalock 1404-A, Baltimore, Maryland 21287-4961.

25% decrease in PVR.[7-9] In preconstricted, isolated, perfused rabbit lungs, amrinone has been shown to decrease PVR by as much as 74%.[10] However, the extent to which amrinone alters the pulmonary vascular pressure-flow relationship in a conscious animal model is unknown.

The goal in the present study was to investigate the effects of amrinone on the left pulmonary vascular pressure-flow ($LP\dot{Q}$) relationship in chronically instrumented conscious dogs. We assessed the dose-response characteristics of amrinone on the $LP\dot{Q}$ relationship in conscious control dogs with and without acute preconstriction of the pulmonary circulation with the thromboxane analog U46619. We repeated these studies in a second group of conscious dogs that had undergone left lung autotransplantation 2–4 weeks before experimentation. We tested two hypotheses: (1) amrinone would have no effect on the baseline $LP\dot{Q}$ relationship in conscious control dogs, and (2) amrinone would cause active, flow-independent pulmonary vasodilation both in the setting of a chronic increase in PVR associated with left lung autotransplantation (LLA)[11] and after acute preconstriction with U46619 in control and post-LLA dogs.

Methods and Materials

The Institutional Animal Care and Use Committee approved all surgical procedures and experimental protocols.

Experimental Preparation

Thirty-one conditioned, male mongrel dogs were used in this study. Eighteen of these dogs (weight range 24–33 kg, mean 26 kg) served as sham-operated controls. Thirteen dogs (weight range 25–40 kg, mean 32 kg) underwent LLA. Except for the LLA procedure, the surgical preparation, chronic instrumentation, and postoperative care were identical in both groups. Animals were premedicated with morphine sulfate (10 mg, intramuscular) and anesthetized with fentanyl citrate (15 μg/kg, intravenous) and pentobarbital sodium (20 mg/kg, intravenous). The trachea was intubated, and the lungs were mechanically ventilated (15 ml/kg, tidal volume). Halothane (~1.2% end-tidal) was used to maintain anesthesia. Using sterile surgical technique, a left thoracotomy was performed through the fifth intercostal space. A pericardial incision was made ventral to the phrenic nerve. Tygon catheters (1.02 mm internal diameter, Norton, Akron, OH) filled with heparin were inserted into the descending thoracic aorta, both atria, and the main pulmonary artery and were secured with purse-string sutures. A hydraulic occluder (14–18 mm internal diameter, Jones, Silver Springs, MD) was positioned around the right main pulmonary artery.

Left lung autotransplantation was performed by sequential anastomoses of the left pulmonary veins, left main bronchus, and left main pulmonary artery.[11] The left lung was mobilized by making a wide circumhilar pericardial incision. The pulmonary veins (inferior, middle, superior) were individually dissected to their point of confluence with the left atrium and stripped of pericardium. Heparin sulfate (3,000 U, intravenous) was administered, and each vein was serially cross-clamped, divided, and anastomosed with a continuous stitch of 7-0 Prolene suture. The left main bronchus was clamped just distal to the carina, divided, and anastomosed using a continuous stitch of 4-0 Prolene suture. Finally, the left main pulmonary artery was stripped of connective tissue, cross-clamped, divided, and anastomosed with a continuous stitch of 6-0 Prolene suture. Care was taken to avoid air emboli after release of the pulmonary artery cross-clamp. Special attention was paid to avoid purse-stringing of tissue, luminal narrowing and to ensure good intimal apposition at the anastomotic sites. Of the 2–3 h necessary to perform the LLA procedure, only 10–20 min of left pulmonary artery cross-clamp time was required. All dogs had an electromagnetic flow probe (10–12 mm internal diameter, Zepeda, Seattle, WA) placed around the left main pulmonary artery. The pericardial edges were loosely apposed. The free ends of the catheters, hydraulic occluder, and flow probe were exteriorized through the seventh intercostal space and tunnelled subcutaneously to a position between the scapulae. A chest tube, placed in the left hemithorax before closure, was removed on the first postoperative day. Postoperative analgesia (morphine sulfate, 10 mg, intramuscular) was given as needed. All dogs received intraoperative antibiotics (cefazolin, 2 g, intravenous), which were continued for 10 days postoperatively (cephalexin, 2 g/day, oral).

Experimental Measurements

The fluid-filled catheters were attached to strain-gauge manometers (Gould Statham P23) to measure intravascular pressures. Transducers were placed at mid chest at the level of the spine and were referenced to atmospheric pressure. Heart rate was calculated from the phasic aortic pressure recording. The electromag-

netic flow probe was connected to a flowmeter (Zepeda model SWF-4rd) to measure left pulmonary blood flow. The flow probe was calibrated *in vivo* biweekly using the thermal dilution technique. A 7-Fr balloon-tipped pulmonary arterial catheter was inserted percutaneously through an external jugular vein after topical lidocaine anesthesia and advanced to a position 2–3 cm beyond the pulmonic valve while the pressure waveform was monitored. The right pulmonary artery occluder was inflated, which directed total pulmonary blood flow through the left pulmonary artery and flow probe. Multiple thermal dilution measurements of left pulmonary blood flow were obtained (American Edwards model 9520A, Irvine, CA) using iced 5-ml injectates of 5% dextrose in water. At least 10 consecutive measurements with less than 10% variability were made randomly throughout the respiratory cycle. Left pulmonary blood flow values have been referenced to body weight ($ml \cdot min^{-1} \cdot kg^{-1}$). Arterial and mixed venous blood samples were withdrawn through the aortic and pulmonary arterial catheters, respectively, for determination of P_{O_2}, P_{CO_2}, pH (Radiometer ABL-3, Copenhagen, Denmark), and oxyhemoglobin saturation (S_{O_2}) (Radiometer Hemoximeter OSM-3).

Experimental Protocols

All experiments were performed with each healthy, unsedated, conscious dog lying on its right side in a quiet laboratory environment. Continuous $LP\dot{Q}$ plots were used to assess the vasoactive effects of amrinone on the pulmonary circulation. Left pulmonary vascular pressure-flow plots were generated by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure/left atrial pressure [PAP/LAP]) and left pulmonary blood flow ($L\dot{Q}$) during gradual (~1 min) inflation of the hydraulic occluder around the right pulmonary artery. This technique to measure the $LP\dot{Q}$ relationship in conscious dogs has little or no effect on systemic hemodynamics, systemic arterial and mixed venous blood gases, or the zonal condition of the lung.[12]

In protocol 1, we tested the hypothesis that amrinone would alter the baseline (no drug) $LP\dot{Q}$ relationship in control dogs to cause pulmonary vasodilation. For each conscious dog (n = 10), $LP\dot{Q}$ plots were generated on the same day without prior drug administration and after the intravenous administration of amrinone (750 $\mu g/kg$ loading dose over 3 min plus cumulative [~15 min at each dose] maintenance infusions of 1, 2, 5, 10, and 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Maintenance infusions in this dosage range have been recommended by the manufacturer and used in several clinical studies.[4,6]

In protocol 2, we tested the hypothesis that amrinone would cause active, flow-independent pulmonary vasodilation in control dogs during acute pulmonary vasoconstriction. For each conscious dog (n = 9), $LP\dot{Q}$ plots were constructed on the same day without prior drug administration, after the intravenous administration of the thromboxane analog U46619, at a dose (0.13 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$) that approximately doubled baseline PAP/LAP for a given value of $L\dot{Q}$, and after the intravenous administration of amrinone as described in protocol 1.

In protocol 3, we tested the hypothesis that amrinone would alter the baseline (no drug) $LP\dot{Q}$ relationship to cause pulmonary vasodilation in the setting of a chronic increase in PVR associated with LLA.[11] Experiments were performed 2–4 weeks after LLA. For each conscious dog (n = 8), $LP\dot{Q}$ plots were constructed on the same day without prior drug administration and after the intravenous administration of amrinone as described in protocol 1.

In protocol 4, we tested the hypothesis that amrinone would cause active, flow-independent pulmonary vasodilation after acute U46619-induced preconstriction in post-LLA dogs. For each conscious dog (n = 8), $LP\dot{Q}$ plots were constructed on the same day without prior drug administration, after the intravenous infusion of U46619 (0.19 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and after the intravenous administration of amrinone as described in protocol 1. The dose of U46619 was titrated to achieve the same degree of acute U46619-induced preconstriction as measured in the control group.

Drug Preparation

U46619 (9,11-dideoxy-11α,9α-epoxymethanoprostaglandin $F_{2\alpha}$, Upjohn, Kalamazoo, MI) suspended in 95% ethanol was stored at −20° C. On the day of the study, 360 μg was dissolved in 60 ml of 0.9% saline. Amrinone (Sterling-Winthrop, Rensselaer, NY) was dissolved in normal saline. All solutions were prepared on the day of the experiment.

Data Analysis

Phasic and mean vascular pressures and $L\dot{Q}$ were displayed continuously on an eight-channel stripchart recorder (Gould Brush model 2800, Eastlake, OH). Mean pressures and $L\dot{Q}$, measured at end-expiration, were obtained with the use of passive electronic filters with a 2-s time constant. All vascular pressures were refer-

enced to atmospheric pressure before and after each LPQ̇ plot. The analog pressure and flow signals also were digitally converted and multiplexed (Medical Systems PCM-8, Greenvale, NY) and stored on videotape (Sharp VCR model VC-H857U) for later playback and analysis. The LPQ̇ relationship was linear by inspection over the empirically measured range of LQ̇. Thus, linear regression analysis was used to calculate the slope and intercept for PAP/LAP (or PAP/0 if LAP <0 mmHg) as a function of LQ̇ in each individual experiment. The correlation coefficient for each protocol averaged 0.98 or higher. Bivariate analysis of variance in the form of Hotelling's $T^{2\,13}$ and one-way analysis of variance were used to assess changes in the LPQ̇ plots in response to amrinone. Student's *t* test for paired comparisons was used to assess changes in steady-state hemodynamics and blood gases. All values are presented as mean ± SE.

Results

Effects of Amrinone on the Pulmonary Vascular LPQ̇ Relationship in Control Dogs

The effects of intravenous amrinone (750 μg/kg loading dose plus 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintenance infusion) on the baseline (no drug) LPQ̇ relationship in conscious control dogs are summarized in figure 1. Amrinone had no significant effect on PAP/LAP at any common value of LQ̇ compared to the no-drug condition; *i.e.*, amrinone did not cause pulmonary vasodilation. The thromboxane analog U46619 caused a shift in the LPQ̇ relationship indicative of acute preconstriction in control conscious dogs (fig. 2). After acute preconstriction with U46619, amrinone decreased PAP/LAP at each common value of LQ̇; *i.e.*, amrinone caused active, flow-independent pulmonary vasodilation (fig. 2). Figure 3 summarizes the pulmonary vascular responses to increasing maintenance infusions of amrinone under baseline (no drug) conditions and after acute preconstriction with U46619. Amrinone had no effect on the baseline LPQ̇ relationship but caused a decrease in PAP/LAP with each dose after acute preconstriction with U46619. At the highest dose, eight of nine conscious control dogs exhibited a pulmonary vasodilator response to amrinone, as reflected by a 24 ± 7% reversal of U46619 preconstriction.

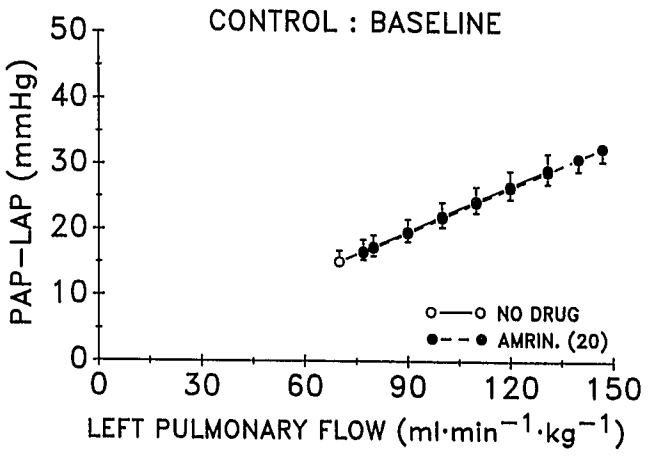

Fig. 1. Effects of amrinone (750 μg/kg loading dose plus 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintenance infusion, intravenous) on the baseline (no drug) left pulmonary vascular pressure-flow relationship (n = 10) in conscious control dogs. Amrinone had no effect on the pulmonary vascular pressure gradient (pulmonary arterial pressure/left atrial pressure [PAP/LAP]) at any value of left pulmonary blood flow (LQ̇).

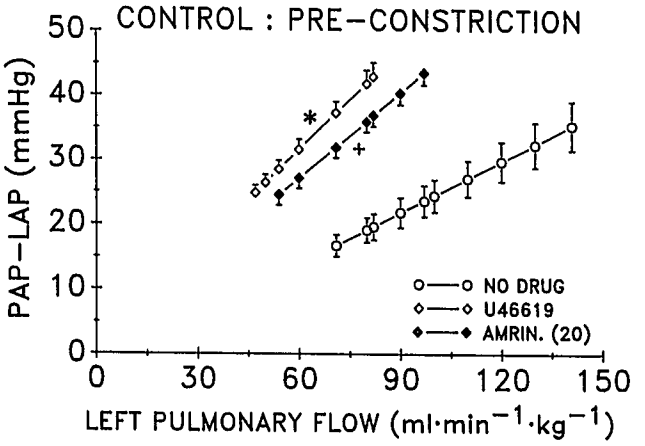

Fig. 2. Effects of U46619 (0.13 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous) on the baseline (no drug) left pulmonary vascular pressure-flow relationship and effects of amrinone (750 μg/kg loading dose plus 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintenance infusion, intravenous) after acute preconstriction with U46619 in nine conscious control dogs. U46619 increased (*$P < 0.01$) pulmonary arterial pressure/left atrial pressure (PAP/LAP) at each common value of LQ̇, *i.e.*, U46619 caused acute pulmonary vasoconstriction. After acute preconstriction, amrinone decreased (†$P < 0.05$) PAP/LAP at each common value of LQ̇, *i.e.*, amrinone caused active, flow-independent pulmonary vasodilation.

The effects of amrinone on steady-state hemodynamics and blood gases are summarized in tables 1 and 2, respectively. Without acute preconstriction, amrinone decreased mixed venous P_{CO_2}. Compared to the no-drug condition, U46619 increased systemic arterial pressure and PAP, and decreased LQ̇, heart rate, and mixed venous pH, P_{O_2}, and S_{O_2}. After acute preconstriction, amrinone increased LQ̇ and heart rate and decreased LAP and systemic arterial and mixed venous P_{CO_2}.

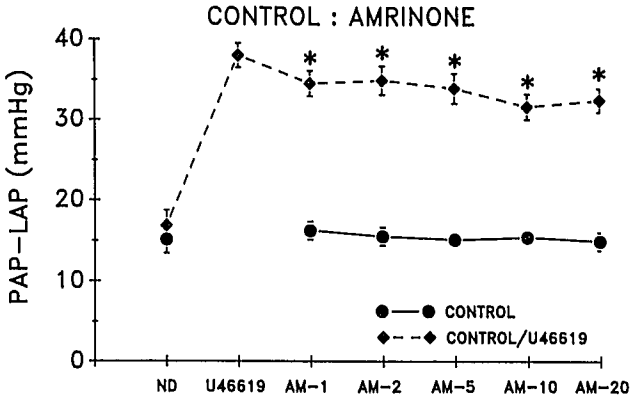

Fig. 3. Effects of increasing maintenance infusions of amrinone measured in 10 conscious control dogs without preconstriction and in 9 conscious control dogs after acute preconstriction with U46619. Values of pulmonary arterial pressure/left atrial pressure (PAP/LAP) at $\dot{L}Q$ of 70 ml · min^{-1} · kg^{-1} are presented for the no-drug condition (ND), after acute U46619 preconstriction, and during cumulative doses (μg · kg^{-1} · min^{-1}) of amrinone (AM). Amrinone had no effect on PAP/LAP without preconstriction. However, after acute preconstriction with U46619, each dose of amrinone caused pulmonary vasodilation (*$P < 0.05$).

Effects of LLA on the Control LP$\dot{Q}$ Relationship

The baseline (no drug) LP$\dot{Q}$ relationship in 10 conscious control dogs and in 8 conscious dogs that had undergone LLA 2–4 weeks earlier are summarized in figure 4. Pulmonary arterial pressure/left atrial pressure was significantly increased at each common value of $\dot{L}Q$ after LLA compared to control dogs, *i.e.*, LLA caused a striking, chronic increase in PVR.

Effects of Amrinone on the LP$\dot{Q}$ Relationship after LLA

The effects of intravenous amrinone (750 μg/kg loading dose plus 20 μg · kg^{-1} · min^{-1} maintenance infusion) on the baseline (no drug) LP$\dot{Q}$ relationship after LLA are summarized in figure 5. Despite a chronic increase in PVR, amrinone had no significant effect on PAP/LAP at any common value of $\dot{L}Q$ compared to the no-drug condition, *i.e.*, amrinone did not cause pulmonary vasodilation. We hypothesized that the chronic shift in the LP$\dot{Q}$ relationship after LLA partially could reflect a passive increase in PVR (*e.g.*, due to loss of vascular surface area) rather than an active increase in vasomotor tone. If active vasomotor tone was not increased after LLA, this could account for the failure of amrinone to alter the baseline LP$\dot{Q}$ relationship. To investigate this possibility, we reexamined the pulmonary vascular response to amrinone after LLA following acute U46619-induced preconstriction. As summarized in figure 6, after acute preconstriction with U46619, amrinone decreased PAP/LAP at each common value of $\dot{L}Q$; *i.e.*, amrinone caused active, flow-independent pulmonary vasodilation. Figure 7 summarizes the pulmonary vascular responses to increasing maintenance infusions of amrinone after LLA with and without acute preconstriction with U46619. In contrast to the absence of an effect on the baseline LP$\dot{Q}$ relationship, amrinone decreased PAP/LAP with each dose after acute preconstriction. At the highest dose, eight of eight conscious post-LLA dogs exhibited a pulmonary vasodilator response to amrinone, as reflected by a 27 ± 10% reversal of U46619 preconstriction. The mag-

Table 1. Steady State Hemodynamics: Control Group

	Protocol	No Drug	U46619	Amrinone (20)
SAP (mmHg)	1	104 ± 4	—	103 ± 3
	2	108 ± 5	122 ± 4*	117 ± 4
PAP (mmHg)	1	17 ± 1	—	18 ± 1
	2	17 ± 1	27 ± 2*	26 ± 1
LAP (mmHg)	1	2.9 ± 0.7	—	2.6 ± 0.7
	2	2.8 ± 0.5	2.9 ± 0.6	0.9 ± 0.8†
$\dot{L}Q$ (ml · min^{-1} · kg^{-1})	1	70 ± 6	—	77 ± 6
	2	71 ± 8	47 ± 3*	54 ± 3†
HR (beats/min)	1	89 ± 5	—	92 ± 4
	2	91 ± 4	77 ± 5*	92 ± 7†

Amrinone was administered intravenously as a 750 μg/kg bolus followed by a 20 μg · kg^{-1} · min^{-1} maintenance infusion.

HR = heart rate; LAP = left atrial pressure; $\dot{L}Q$ = left pulmonary flow; PAP = pulmonary arterial pressure; SAP = systemic arterial pressure.

* $P < 0.05$ *versus* no drug.

† $P < 0.05$ *versus* U46619.

Table 2. Steady State Blood Gases: Control Group

	Protocol	No Drug	U46619	Amrinone (20)
Systemic arterial				
pH	1	7.37 ± 0.01	—	7.38 ± 0.01
	2	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 0.01
P_{CO_2} (mmHg)	1	38 ± 1	—	38 ± 1
	2	36 ± 1	34 ± 1	32 ± 1†
P_{O_2} (mmHg)	1	99 ± 3	—	101 ± 4
	2	102 ± 3	96 ± 4	98 ± 3
S_{O_2} (%)	1	94.2 ± 0.4	—	94.6 ± 0.5
	2	95.9 ± 0.6	95.7 ± 0.8	95.9 ± 0.7
Mixed venous				
pH	1	7.36 ± 0.01	—	7.35 ± 0.01
	2	7.36 ± 0.01	7.34 ± 0.01*	7.36 ± 0.01
P_{CO_2} (mmHg)	1	43 ± 1	—	41 ± 1*
	2	41 ± 1	40 ± 1	38 ± 1†
P_{O_2} (mmHg)	1	50 ± 1	—	48 ± 1
	2	46 ± 2	42 ± 2*	43 ± 2
S_{O_2} (%)	1	69.1 ± 1.1	—	69.5 ± 1.3
	2	71.5 ± 1.4	65.5 ± 2.2*	65.8 ± 1.6

P_{CO_2} = carbon dioxide tension; P_{O_2} = oxygen tension; S_{O_2} = oxygen saturation.

* $P < 0.05$ *versus* no drug.

† $P < 0.05$ *vesus* U46619.

nitude of amrinone-induced pulmonary vasodilation after acute preconstriction was similar in the control and post-LLA groups.

As summarized in tables 3 and 4, without acute U46619-induced preconstriction, amrinone decreased steady-state LAP and systemic arterial P_{CO_2}. Compared to the no-drug condition, U46619 increased systemic arterial pressure, PAP, and mixed venous P_{CO_2} and decreased $\dot{LQ}$, heart rate, systemic arterial and mixed venous pH, P_{O_2}, and S_{O_2}. After U46619 preconstriction,

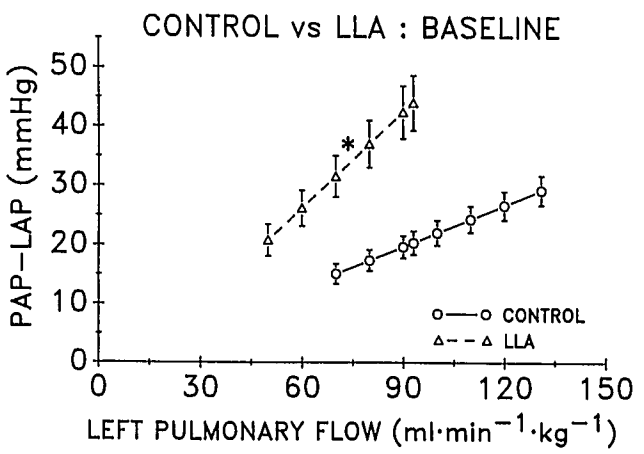

Fig. 4. Composite left pulmonary vascular pressure-flow plots measured in 10 conscious control dogs and in 8 conscious dogs that had undergone left lung autotransplantation (LLA) 2–4 weeks earlier. Pulmonary arterial pressure/left atrial pressure was significantly increased (*$P < 0.01$) after LLA at each common value of $\dot{LQ}$ compared to control dogs, *i.e.*, LLA caused a striking, chronic increase in pulmonary vascular resistance.

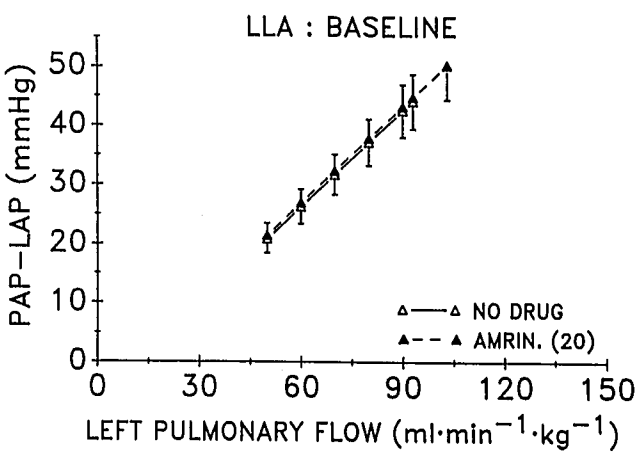

Fig. 5. Effects of amrinone (750 μg/kg loading dose plus 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintenance infusion, intravenous) on the baseline (no drug) left pulmonary vascular pressure-flow relationship (n = 8) in conscious dogs 2–4 weeks after left lung autotransplantation. Amrinone had no effect on PAP/LAP at any value of $\dot{LQ}$.

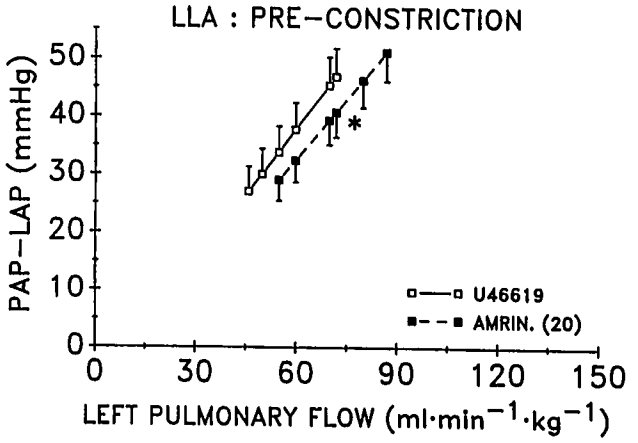

Fig. 6. Effects of amrinone (750 μg/kg loading dose plus 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintenance infusion, intravenous) after acute preconstriction with U46619 (n = 8) in conscious dogs 2–4 weeks after left lung autotransplantation. After acute preconstriction, amrinone decreased (*$P < 0.01$) PAP/LAP at each common value of LQ̇, *i.e.*, amrinone caused active, flow-independent pulmonary vasodilation.

amrinone increased LQ̇ and heart rate and decreased LAP and systemic arterial and mixed venous P_{CO_2}.

Discussion

This is the first study to investigate the effects of amrinone on the pulmonary circulation in conscious control dogs and in conscious dogs after LLA. Our experimental approach has several important features. First, the use of chronically instrumented, conscious dogs avoided the confounding effects of acute surgical trauma and general anesthesia on pulmonary vascular regulation. General anesthesia has been shown to modify neural,[14,15] humoral,[16,17] and local[18,19] mechanisms of pulmonary vascular regulation. Second, the use of LPQ̇ plots allowed us to distinguish between vasoactive and passive (flow-dependent) effects of amrinone on the pulmonary circulation. Moreover, this technique permits the rapid generation of LPQ̇ plots without significant perturbations in systemic hemodynamics or blood gases, which makes this experimental model amenable to the study of dose-response relationships. Third, utilization of the LLA model[11] allowed us to assess the pulmonary vascular effects of amrinone in the setting of a chronic increase in PVR. Finally, pretreating both control and post-LLA conscious dogs with the thromboxane analog U46619 allowed us to assess the pulmonary vascular effects of amrinone in the setting of acute pulmonary vasoconstriction. The results of this study indicate that amrinone has no effect on the baseline (no drug) LPQ̇ relationship in conscious control dogs or conscious dogs with a chronic increase in PVR after LLA. However, amrinone exerts a pulmonary vasodilator effect in these two groups after acute preconstriction with U46619.

The failure to observe a pulmonary vasodilator response to amrinone in control dogs probably reflects the low state of vasomotor tone in these healthy conscious dogs. As we have reported previously,[11] LLA caused a chronic increase in PVR. A component of this

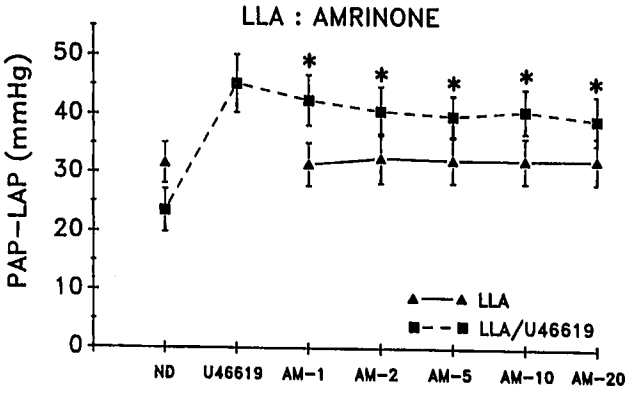

Fig. 7. Effects of increasing maintenance infusions of amrinone measured in eight conscious dogs after left lung autotransplantation (LLA) and in eight dogs after LLA following acute preconstriction with U46619. Values of PAP/LAP at LQ̇ of 70 $ml \cdot min^{-1} \cdot kg^{-1}$ are presented for the no-drug condition (ND), after acute U46619 preconstriction, and during cumulative doses ($\mu g \cdot kg^{-1} \cdot min^{-1}$) of amrinone (AM). Amrinone had no effect on PAP/LAP without acute preconstriction. However, after acute preconstriction with U46619, each dose of amrinone caused pulmonary vasodilation (*$P < 0.05$).

Table 3. Steady State Hemodynamics: LLA Group

	Protocol	No Drug	U46619	Amrinone (20)
SAP (mmHg)	3	103 ± 3	—	103 ± 4
	4	105 ± 5	125 ± 6*	122 ± 9
PAP (mmHg)	3	23 ± 4	—	23 ± 5
	4	22 ± 4	31 ± 3*	30 ± 3
LAP (mmHg)	3	3.3 ± 1.1	—	2.0 ± 0.8*
	4	3.6 ± 0.5	5.2 ± 1.4	1.1 ± 1.1†
LQ̇ ($ml \cdot min^{-1} \cdot kg^{-1}$)	3	50 ± 4	—	51 ± 6
	4	61 ± 6	47 ± 4*	55 ± 5†
HR (beats/min)	3	93 ± 7	—	100 ± 10
	4	92 ± 6	81 ± 7*	96 ± 7†

HR = heart rate; LAP = left atrial pressure; LQ̇ = left pulmonary flow; PAP = pulmonary arterial pressure; SAP = systemic arterial pressure.

* $P < 0.05$ *versus* no drug.

† $P < 0.05$ *versus* U46619.

Table 4. Steady State Blood Gases: LLA Group

	Protocol	No Drug	U46619	Amrinone (20)
Systemic arterial				
pH	3	7.39 ± 0.01	—	7.39 ± 0.01
	4	7.39 ± 0.01	7.36 ± 0.01*	7.36 ± 0.01
P_{CO_2} (mmHg)	3	35 ± 1	—	33 ± 1*
	4	36 ± 1	36 ± 1	33 ± 1†
P_{O_2} (mmHg)	3	103 ± 4	—	109 ± 8
	4	107 ± 5	95 ± 7*	93 ± 5
S_{O_2} (%)	3	95.5 ± 0.7	—	93.5 ± 1.3
	4	95.8 ± 0.3	93.1 ± 1.1*	93.9 ± 1.1
Mixed venous				
pH	3	7.38 ± 0.01	—	7.37 ± 0.01
	4	7.37 ± 0.01	7.33 ± 0.01*	7.33 ± 0.01
P_{CO_2} (mmHg)	3	38 ± 1	—	38 ± 1
	4	40 ± 1	43 ± 2*	39 ± 2†
P_{O_2} (mmHg)	3	50 ± 2	—	50 ± 2
	4	50 ± 2	47 ± 3*	43 ± 2
S_{O_2} (%)	3	73.4 ± 1.7	—	69.5 ± 2.1
	4	69.9 ± 2.1	60.3 ± 2.3*	61.2 ± 2.9

P_{CO_2} = carbon dioxide tension; P_{O_2} = oxygen tension; S_{O_2} = oxygen saturation.

* $P < 0.05$ *versus* no drug.

† $P < 0.05$ *vesus* U46619.

increase in PVR is due to "denervation supersensitivity" of sympathetic α_1 adrenoreceptors after LLA.[20] An additional mechanism may involve a defect in endothelium-dependent pulmonary vasodilation after LLA.[21] Our prediction was that amrinone would exert a pulmonary vasodilator influence in this setting of increased PVR after LLA. However, an amrinone-induced vasodilator response was observed only after acute preconstriction with U46619. This result suggests that the chronic increase in PVR after LLA also may include a significant passive component. One possibility is that LLA results in a decrease in vascular surface area because of leukocyte plugging, thrombus formation, or rarefaction of the pulmonary vasculature. A detailed morphologic study is required to document this possibility. If this effect is an inevitable consequence of the surgical transplantation procedure, it could have important clinical implications.

Amrinone caused pulmonary vasodilation in both groups after acute preconstriction with U46619. This result is consistent with human and animal studies.[3-10] However, the results of previous studies are limited by several factors. The human studies[3,4,6] were performed in anesthetized patients, and the effects of amrinone were assessed by single-point calculations of PVR rather than shifts in the pulmonary vascular pressure-flow relationship. The animal studies[7-9] assessed the effects of bolus administration of amrinone; therefore, the sustained effects of amrinone associated with maintenance infusions could not be evaluated.

In summary, amrinone does not exert a vasodilator influence on the baseline LP$\dot{Q}$ relationship in conscious control dogs or post-LLA dogs with a chronic increase in PVR. However, amrinone causes active, flow-independent pulmonary vasodilation in both groups of conscious dogs after acute preconstriction with the thromboxane analog U46619. The magnitude of amrinone-induced pulmonary vasodilation is less than that observed in response to other pulmonary vasodilators (*e.g.*, sodium nitroprusside) in both conscious control dogs and conscious dogs after LLA.[11,21] Extrapolation of results across species should be done with caution. However, these results appear to support the use of amrinone as a therapeutic modality in the setting of acute pulmonary vasoconstriction and to indicate that the vasodilator efficacy of amrinone depends on the mechanism responsible for the underlying pulmonary vascular abnormality.

The authors thank Rosie Cousins and Dr. B. X. Tong for their technical work and Lisa DeLoriers and Gary Vornheder for the preparation of this manuscript.

References

1. Hayes JS, Bowling N, Boder GB, Kauffman R: Molecular basis for the cardiovascular activities of amrinone and AR-L57. J Pharmacol Exp Ther 230:124–132, 1984

2. Bottorff MB, Rutledge DR, Pieper JA: Evaluation of intravenous amrinone: The first of a new class of positive inotropic agents with vasodilator properties. Pharmacotherapy 5:227–237, 1985

3. Konstam MA, Cohen SR, Salem DN, Das D, Aronovitz MJ, Brockway BA: Effect of amrinone on right ventricular function: Predominance of afterload reduction. Circulation 74:359–366, 1986

4. Hermiller JB, Leithe ME, Magorien RD, Unverferth DV, Leier CV: Amrinone in severe congestive heart failure: Another look at an intriguing new cardioactive drug. J Pharmacol Exp Ther 228:319–326, 1983

5. Hess W, Arnold B, Veit S: The haemodynamic effects of amrinone in patients with mitral stenosis and pulmonary hypertension. Eur Heart J 7:800–807, 1986

6. Deeb GM, Bolling SF, Guynn TP, Nicklas JM: Amrinone versus conventional therapy in pulmonary hypertensive patients awaiting cardiac transplantation. Ann Thorac Surg 48:665–669, 1989

7. Coe JY, Olley PM, Vella G, Coceani F: Bipyridine derivatives lower arteriolar resistance and improve left ventricular function in newborn lambs. Pediatr Res 22:422–428, 1987

8. Mammel MC, Einzig S, Kulik TJ, Thompson TR, Lock JE: Pulmonary vascular effects of amrinone in conscious lambs. Pediatr Res 17:720–724, 1983

9. Hill NS, Rounds S: Amrinone dilates pulmonary vessels and blunts hypoxic vasoconstriction in isolated rat lungs. Proc Soc Exp Biol Med 173:205–212, 1983

10. Clarke WR, Morray JP, Powers K, Soltow L: Amrinone reduces pulmonary vascular resistance elevated by U46619 in isolated perfused lungs. J Cardiovasc Pharmacol 18:85–94, 1991

11. Murray PA, Stuart RS, Fraser CD, Fehr DM, Chen BB, Rock P, Desai PM, Nyhan DP: Acute and chronic pulmonary vasoconstriction after left lung autotransplantation in conscious dogs. J Appl Physiol 73:603–609, 1992

12. Nishiwaki K, Nyhan DP, Rock P, Desai PM, Peterson WP, Pribble CG, Murray PA: N^{ω}-nitro-L-arginine and the pulmonary vascular pressure-flow relationship in conscious dogs. Am J Physiol 262: H1331–H1337, 1992

13. Wilkinson L: Systat: The System for Statistics. Evanston, Systat, 1990

14. Chen BB, Nyhan DP, Fehr DM, Murray PA: Halothane anesthesia abolishes pulmonary vascular responses to neural antagonists. Am J Physiol 262:H117–H122, 1992

15. Nyhan DP, Goll HM, Chen BB, Fehr DM, Clougherty PW, Murray PA: Pentobarbital anesthesia alters pulmonary vascular response to neural antagonists. Am J Physiol 256:H1384–H1392, 1989

16. Fehr DM, Nyhan DP, Chen BB, Murray PA: Pulmonary vasoregulation by cyclooxygenase metabolites and angiotensin II after hypoperfusion in conscious, pentobarbital-anesthetized, and halothane-anesthetized dogs. ANESTHESIOLOGY 75:257–267, 1991

17. Nyhan DP, Chen BB, Fehr DM, Murray PA: Anesthesia alters pulmonary vasoregulation by angiotensin II and captopril. J Appl Physiol 72:636–642, 1992

18. Nyhan DP, Chen BB, Fehr DM, Goll HM, Murray PA: Pentobarbital augments pulmonary vasoconstrictor response to cyclooxygenase inhibition. Am J Physiol 257:H1140–H1146, 1989

19. Murray PA, Fehr DM, Chen BB, Rock P, Esther JW, Desai PM, Nyhan DP: Differential effects of general anesthesia on cGMP-mediated pulmonary vasodilation. J Appl Physiol 73:721–727, 1992

20. Nishiwaki K, Nyhan DP, Stuart RS, Desai PM, Peterson WP, Rock P, Pribble CG, Murray PA: Pulmonary vascular α_1 adrenoreceptor activity in conscious dogs after left lung autotransplantation. J Appl Physiol 74:727–735, 1993

21. Nishiwaki K, Nyhan DP, Stuart RS, Rock P, Desai PM, Peterson WP, Murray PA: Abnormal responses to pulmonary vasodilators in conscious dogs after left lung autotransplantation. Am J Physiol 264: H917–H925, 1993