Cardiothoracic Anesthesia, Respiration and Airway

Selective pulmonary vasodilation with inhaled aerosolized milrinone in heart transplant candidates

[La vasodilatation pulmonaire sélective avec l'inhalation de milrinone en aérosol chez des candidats à la greffe cardiaque]

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Purpose: Selective pulmonary vasodilation is an advantageous method for testing the responsiveness of the pulmonary vasculature of heart transplant candidates. A pilot study was undertaken to test the hypothesis that inhaled aerosolized milrinone may cause selective pulmonary vasodilation.

Methods: 18 consecutive male heart transplant candidates with either dilated or ischemic cardiomyopathy were included in this open clinical study. Nine of the patients had significant pulmonary hypertension with a mean pulmonary arterial pressure > 30 mmHg. After baseline measurements, 2 mg of milrinone was administered by ultrasonic nebulization. Pulmonary and systemic hemodynamics were measured ten, 30, and 60 min after inhalation.

Results: After inhalation for ten minutes, milrinone induced a significant reduction of mean pulmonary arterial pressure (32.7 ± 9.1 vs 37.7 ± 7.5 mmHg, $P = 0.01$), pulmonary vascular resistance index (296 ± 150 vs 396 ± 151 dyn·sec⁻¹·cm⁻⁵·m², $P = 0.02$) and transpulmonary gradient (10.6 ± 5.5 vs 15 ± 4.9 , $P = 0.01$) only in patients with significant pulmonary hypertension. There was no significant effect on mean arterial pressure or systemic vascular resistance at any time after inhalation in either group. Furthermore, there was no influence on extravascular lung water or intrathoracic blood volume.

Conclusions: We conclude that inhaled aerosolized milrinone for a short period selectively dilates the pulmonary vasculature in heart transplant candidates with elevated pulmonary arterial pressure, without producing systemic side effects. Further comparative studies are necessary to evaluate possible advantages of milrinone compared to other inhaled vasodilators.

Objectif: La vasodilatation pulmonaire sélective permet de vérifier avantageusement la réactivité du système vasculaire pulmonaire des candidats à la greffe cardiaque. Nous avons vérifié si l'inhalation de milrinone en aérosol pouvait causer une vasodilatation pulmonaire sélective.

Méthode: Ont été inclus dans notre étude clinique ouverte 18 hommes, candidats à la greffe cardiaque, atteints de cardiomyopathie de dilatation ou ischémique. Neuf d'entre eux présentaient une hypertension artérielle pulmonaire moyenne > 30 mmHg. Après les mesures de base, nous avons administré 2 mg de milrinone avec une nébulisation par ultrasons. L'hémodynamique pulmonaire et générale ont été mesurées à 10, 30 et 60 min après l'inhalation.

Résultats: Après avoir été inhalée pendant 10 min, la milrinone a réduit significativement la tension artérielle pulmonaire moyenne ($32,7 \pm 9,1$ vs $37,7 \pm 7,5$ mmHg, $P = 0,01$), l'index de résistance vasculaire pulmonaire (296 ± 15 vs 396 ± 151 dyn·s⁻¹·cm⁻⁵·m², $P = 0,02$) et le gradient transpulmonaire ($10,6 \pm 5,5$ vs $15 \pm 4,9$, $P = 0,01$) dans les cas d'hypertension artérielle pulmonaire significative. Après l'inhalation, il n'y a pas eu d'effet significatif sur la tension artérielle moyenne ou la résistance vasculaire générale pour tous les temps de mesure chez les patients des deux groupes. Et, il n'y a pas eu d'influence sur le liquide pulmonaire extravasculaire ou le volume sanguin intrathoracique.

Conclusion: L'inhalation de milrinone en aérosol pendant une courte période produit une dilatation sélective du système vasculaire pulmonaire chez des candidats à la greffe cardiaque qui présentent une tension artérielle pulmonaire élevée, sans produire d'effets secondaires généralisés. Il reste à évaluer les avantages possibles de la milrinone comparée à d'autres vasodilatateurs inhalés.

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Assessed December 20, 2004.

Accepted April 18, 2005.

Final revision accepted June 24, 2005.

AN elevated pulmonary vascular resistance (PVR) or transpulmonary gradient (TPG) contributes to increased mortality following orthotopic heart transplantation caused by postoperative right heart failure.^{1,2} Preoperative evaluation of the reversibility of elevated pulmonary resistance in response to vasodilator therapy is important for the postoperative management of right heart failure.³ Consequently, measurement of pulmonary hemodynamics is a routine procedure in the assessment of potential transplantation recipients.

In patients with elevated PVR, drugs such as nitrates, sodium nitroprusside, or prostacyclin (PGI₂) are used to determine whether the abnormalities of the pulmonary vascular bed are reversible or not. However, the use of *iv* vasodilators is often limited by systemic hypotension.⁴ Inhaled nitric oxide (NO), PGI₂, and iloprost have been shown to act as selective pulmonary vasodilators without systemic effects, in patients with primary and secondary pulmonary hypertension (PH) as well.^{5–8} Unfortunately, NO is a toxic molecule and requires specialized delivery systems and monitoring due to the production of methemoglobin and higher oxides of nitrogen.⁹ Because of its short half-life, NO has to be administered continuously, and even brief interruptions may cause a dangerous rebound of PH.¹⁰ The advantages of inhaled PGI₂ and iloprost include a lack of toxic reactions and ease of administration.^{7,11} On the other hand, Haraldsson *et al.* found no improved effects on hemodynamic variables, comparing inhaled PGI₂ with inhaled NO in the evaluation of heart transplant candidates.⁶

Currently, there exists little information regarding the use of milrinone by inhalation. The drug is an adenosine-3',5'-cyclic monophosphate (cAMP)-selective phosphodiesterase enzyme (PDE) inhibitor. Haraldsson *et al.* demonstrated that inhaled milrinone, in incremental concentrations, was able to reduce PVR in postoperative cardiac surgical patients with PH.¹² Pamboukian *et al.* used an intravenously administered milrinone-bolus in the assessment of patients with congestive heart failure and PH.¹³ Based upon the published data of Haraldsson *et al.* and our own clinical experiences with inhaled milrinone in patients with right heart failure, we undertook a pilot study to investigate the effects of inhaled aerosolized milrinone on pulmonary and systemic hemodynamics in the evaluation of patients with planned heart transplantation.

Patients and methods

The study was designed as a prospective, non-randomized, open clinical trial. The protocol was approved by

the Human Ethics Committee of the Medical Faculty, University of Halle-Wittenberg. Eighteen consecutive male patients scheduled for diagnostic right heart catheterization were included in the study after giving informed consent. The diagnoses were ischemic ($n = 8$) or dilated ($n = 10$) cardiomyopathy. Patients received their usual regimen of oral medication on the morning of the study, and no additional sedation was given during insertion of lines or the study period.

In accordance with the American College of Chest Physicians evidence-based clinical practice guidelines for diagnosis of PH, patients were assigned to the PH group, or the non-pulmonary hypertension (nonPH)-group.¹⁴

For inhalation of aerosolized milrinone, an ultrasonic nebulizer (Opti-Neb®, Nebu-tec GmbH, Elsenfeld, Germany) was used. The nebulized particle size ranges from 3 to 5 μm with this device. Two milligrams of milrinone (dissolved in dextrose) were diluted in 3 mL 0.9% sodium chloride, and inhalation was complete within 15 min. Our decision to use a dose of milrinone 2 mg was based upon the recommendations for the loading dose of milrinone in patients with severe heart failure (25–50 $\mu\text{g}\cdot\text{kg}^{-1}$) and a previous report of Haraldsson *et al.* who investigated a dose of 3 mg.¹² In consideration of the different outputs of nebulizers used in both studies (jet nebulizer in the study of Haraldsson *et al.* *vs* ultrasonic nebulizer in our study) the dose was reduced to 2 mg in our study.

Measurements of hemodynamics were performed using a radial artery catheter (PICCO, Pulsion GmbH, Munich, Germany) and a pulmonary artery catheter (model: CCO-V-CCO/CEDV/177F75, Edwards Lifesciences, Irvine, CA, USA), inserted via the left internal jugular vein. The following variables were measured or calculated: systolic, diastolic, and mean arterial blood pressure (MAP), heart rate (HR), systolic, diastolic, and mean pulmonary artery pressure (MPAP), central venous pressure, pulmonary capillary wedge pressure (PCWP), stroke volume, systemic vascular resistance (SVR) and PVR. Cardiac output was measured, cardiac index, pulmonary and SVR indices (PVRI, SVRI), stroke index, right ventricular ejection fraction (REF), intrathoracic blood volume (ITBV), and extravascular lung water (EVLW) were calculated.

The methodology of REF measurement uses the slaved electrocardiograph signal and generates a relaxation waveform which resembles the bolus thermodilution washout decay curve. Calculation of REF is based on estimation of the exponential decay time constant (τ) of this curve and HR: $\text{REF} = 1 - \exp(-60/[\tau \times \text{HR}])$.¹⁵ Single thermodilution ITBV and

TABLE I Patient characteristics and preoperative medications

Group variables	PH	nonPH n = 9	P-value n = 9
Age (yr)	47.9 ± 9	44.7 ± 11.2	n.s.
Height (cm)	177 ± 4.4	175.1 ± 10.5	n.s.
Weight (kg)	84.4 ± 14.3	76.8 ± 14.5	n.s.
BSA (m ²)	2.1 ± 0.2	1.9 ± 0.2	n.s.
Dilated CMP (n)	6	5	n.s.
Ischemic CMP (n)	3	4	n.s.
Previous CABG (n)	4	4	n.s.
AICD (n)	4	5	n.s.
ACE-Inhibitors (n)	9	9	n.s.
Nitrates (n)	4	4	n.s.
β-Blockers (n)	7	6	n.s.
Diuretics (n)	7	5	n.s.
Antiarrhythmics (n)	5	2	P < 0.05
Calcium channel blockers (CCB) (n)	4	2	n.s.
Digitalis (n)	7	7	n.s.

BSA = body surface area; PH = pulmonary hypertension; CMP = cardiomyopathy; CABG = coronary artery bypass graft; AICD = automatic internal cardioverter defibrillator; ACE = angiotensin converting enzyme.

EVLW were calculated according to the formula described by Sakka *et al.*: ITBV = (1.25 global end-diastolic volume) – 28.4 (mL) and EVLW = intrathoracic thermal volume – ITBV (mL).¹⁶

All parameters were measured at baseline and at the end of each evaluation period. Triplicate measurements were averaged for each reported cardiac output.

Statistics

Statistical analysis was made by an independent bureau of statistics (MoRe.data, Giessen, Kerkrader Strasse, Germany). The data are presented as mean values and SD. After testing for normal distribution with the Shapiro-Wilk test, comparison of data (values 10, 30, and 60 min after inhalation) with baseline was undertaken by non-parametric Wilcoxon test followed by Bonferroni correction. The Mann-Whitney U test was used to compare baseline values between the PH- and nonPH-groups. A *P*-value < 0.05 was considered to indicate statistical significance.

Results

Eighteen adult male patients completed the study protocol. Pulmonary artery pressures for the two groups were: PH-group: (*n* = 9) MPAP 37.7 ± 7.5 mmHg and nonPH-group: (*n* = 9) MPAP 20.0 ± 8.5 mmHg. Patient characteristics are shown in Table I. All treated patients tolerated the 2 mg dose of milrinone without

any side effects. No patient experienced deterioration of cardiac function in the post-study course, as documented by transthoracic echocardiography.

The changes of hemodynamic parameters in response to inhalation of milrinone are presented in Table II. In both groups, there were no significant effects of milrinone inhalation on CI, MAP, HR, EVLW, ITBV, SvO₂, and SVRI compared with baseline values. A reduction of MPAP (32.7 ± 9.1 *vs* 37.7 ± 7.5 mmHg, *P* = 0.01, Figure 1), PVRI (296 ± 150 *vs* 396 ± 151 dyn·sec⁻¹·cm⁻⁵·m², *P* = 0.015, Figure 2), and TPG (10.6 ± 5.5 *vs* 15 ± 4.9 mmHg, *P* = 0.012) ten minutes after inhalation of milrinone was observed only in patients with pre-existing PH. These changes were accompanied by a significant increase of REF (38.1 ± 13.5% *vs* 34.4 ± 9.3%, *P* = 0.03) 30 min after inhalation of milrinone. Finally, in patients with PH, PCWP was significantly reduced 30 min after inhalation of milrinone (20.4 ± 6.9 *vs* 22.7 ± 6.3 mmHg, *P* = 0.028, Figure 3), while in the nonPH-group a significant increase of PCWP (11.0 ± 7.1 *vs* 8.9 ± 4.8 mmHg, *P* = 0.04) was seen 30 min after milrinone administration.

Discussion

The use of NO, inhaled PGI₂ and iloprost for evaluation of heart transplant candidates with PH has been described previously, but the use of aerosolized milrinone in these patients has not been studied. The inodilator milrinone is a non-glycosidic, non-sympathomimetic drug which increases myocardial and vascular smooth muscle cAMP concentrations by inhibiting phosphodiesterase fraction III (PDE-III) enzymes, thus modulating intracellular calcium levels with resultant increased myocardial contractility and systemic vasodilation.¹⁷ Due to these properties, PDE-inhibitors represent an important therapeutic option for patients with ventricular dysfunction undergoing cardiac surgery.¹⁸

In recent years, several drugs have been identified for inhaled administration for evaluation of heart transplant candidates, with and without accompanying PH.¹⁹ In our previous investigations we demonstrated that iloprost, the stable analogue of PGI₂, is a pulmonary-selective vasodilator which has several advantages compared to NO, the most important being a lack of adverse reactions and ease of administration.^{8,20}

In the present study we showed that inhaled aerosolized milrinone induces a pulmonary-selective vasodilation in the evaluation of heart transplant candidates with chronic heart failure. Ten minutes after inhalation of 2 mg aerosolized milrinone, patients with PH developed a significant decrease of MPAP,

TABLE II Effect of milrinone-inhalation on systemic and pulmonary hemodynamics in patients with ($n = 9$) and without ($n = 9$) pulmonary hypertension

	Baseline	10 min	30 min	60 min	Significance
HR					
(PH-group)	82 ± 22	83 ± 23	85 ± 24	84 ± 22	n.s.
(nonPH-group)	75 ± 18	73 ± 14	75 ± 16	72 ± 15	n.s.
CI					
(PH-group)	2.8 ± 0.4	2.9 ± 0.4	2.9 ± 0.6	2.7 ± 0.3	n.s.
(nonPH-group)	2.8 ± 0.6	3.1 ± 0.7	3.1 ± 0.7	3.0 ± 0.7	n.s.
MAP					
(PH-group)	80.1 ± 11	79.3 ± 10.4	81.9 ± 12.2	80.9 ± 7.1	n.s.
(nonPH-group)	80.3 ± 13.4	83 ± 14.8	85 ± 17.8	85.2 ± 16.1	n.s.
SVRI					
(PH-group)	2086 ± 339	2078 ± 350	2189 ± 416	2224 ± 251	n.s.
(nonPH-group)	2231 ± 665	2098 ± 585	2173 ± 900	2153 ± 582	n.s.
TPG					
(PH-group)	15 ± 4.9	10.6 ± 5.5*	12.7 ± 5.7	15.2 ± 6.1	* $P = 0.012$
(nonPH-group)	11.1 ± 4.3	8.8 ± 3.4	10.3 ± 5.2	11.1 ± 4.2	n.s.
ITBV					
(PH-group)	2375 ± 754	2404 ± 651	2130 ± 838	2464 ± 492	n.s.
(nonPH-group)	1872 ± 705	2160 ± 810	1965 ± 708	1969 ± 630	n.s.
EVLW					
(PH-group)	1004 ± 495	1104 ± 714	1088 ± 606	1128 ± 616	n.s.
(nonPH-group)	772 ± 327	829 ± 430	895 ± 379	995 ± 771	n.s.
REF					
(PH-group)	34.4 ± 9.3	33.8 ± 12.1	38.1 ± 13.5*	34.6 ± 10.7	* $P = 0.032$
(nonPH-group)	33.8 ± 8.6	32.7 ± 8.5	36.3 ± 7.8	36.9 ± 10.8	n.s.
SvO ₂					
(PH-group)	63.4 ± 9.0	66.8 ± 8.1	65.5 ± 6.8	64.8 ± 8.7	n.s.
(nonPH-group)	66.3 ± 8.9	64.4 ± 6.8	65.7 ± 7.8	66.8 ± 9.4	n.s.

HR = Heart rate ($1 \cdot \text{min}^{-1}$), PH = pulmonary hypertension; CI = cardiac index ($\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$), MAP = mean arterial pressure (mmHg), SVRI = systemic vascular resistance index ($\text{dyn} \cdot \text{sec}^{-1} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$), TPG = transpulmonary gradient (mmHg), ITBV = intrathoracic blood volume (mL), EVLW = extravascular lung water (mL), REF = right ventricular ejection fraction (%), and SvO₂ = mixed venous oxygen saturation (kPa). * $P < 0.05$ compared to baseline.

PVRI and TGP, which lasted for only a short period. There were no effects on systemic hemodynamics: MAP, SVRI, and HR remained unchanged throughout the study period.

Even a short period of vasodilator administration may be associated with an increase in left ventricular filling pressure in patients with heart failure due to an increased pulmonary venous return to a poorly compliant left ventricle, resulting in an acute pulmonary edema, as described by Bocchi *et al.* after inhalation of NO.²¹ In our study, PCWP increased only in the group of patients without pre-existing PH shortly

after inhalation of milrinone, but this was not accompanied by an increase of intrathoracic blood volume or extravascular lung water. In patients with PH, milrinone-inhalation induced a significant reduction of PCWP. This may be a great advantage of PDE-inhibitors compared with NO or prostanoids, especially in the treatment of patients with pulmonary venous hypertension, and may offer a safer and perhaps better approach to patients with an unstable hemodynamic state.

There is limited experience with inhaled use of PDE-inhibitors, but our results are in agreement with

FIGURE 1 Effect of milrinone-inhalation on mean arterial pressure in patients with ($n = 9$) and without ($n = 9$) pulmonary hypertension; * $P < 0.05$ compared to baseline.

FIGURE 2 Effect of milrinone-inhalation on pulmonary capillary wedge pressure in patients with ($n = 9$) and without ($n = 9$) pulmonary hypertension; * $P < 0.05$ compared to baseline.

previously published data of Haraldsson *et al.* They described a dose-dependent pulmonary vasodilation after inhalation of milrinone in patients with PH in the early postoperative course following cardiac surgery with extracorporeal circulation.¹² In their study, the

FIGURE 3 Effect of milrinone-inhalation on pulmonary vascular resistance index in patients with ($n = 9$) and without ($n = 9$) pulmonary hypertension; * $P < 0.05$ compared to baseline.

maximal decrease in PVR by inhaled milrinone (-20%) was comparable to the maximum effect documented in our investigation (-25.3%). The duration of vasodilation in both studies was comparable as well: 20 min after termination of milrinone-inhalation in the study of Haraldsson *et al.*, and after 30 min in our study, MPAP and PVRI returned to baseline values. Despite the fact that different inhalation-devices were used (jet nebulizer *vs* ultrasonic nebulizer in our investigation), the effective dose reaching the alveolar space seems to be comparable. The total dose, administered during the 15-min inhalation period, was 3 mg in the study of Haraldsson *et al.* and 2 mg in our study, indicating that ultrasonic nebulization leads to a higher efficiency and output.^{12,22}

There is only one report evaluating the use of milrinone in the pretransplant assessment of patients with congestive heart failure and PH.¹³ In this study, milrinone was administered as an *iv* bolus at a dose of 50 $\mu\text{g} \cdot \text{kg}^{-1}$, resulting in a significant reduction of PVR, MPAP, and PCWP, combined with a significant increase of cardiac output. Unfortunately, the effects on MAP and SVR were not described. The dose of milrinone evaluated in this study¹³ was the recommended dosage for the treatment of acute left ventricular failure and cardiogenic shock, and may reach 4 mg for a patient weighing 80 kg. Without adequate volume control and replacement, this dose of milrinone may induce systemic hypotension with deterioration of right ventricular coronary perfusion

and performance. This deleterious side effect can be avoided by inhaled administration, as demonstrated by the results of our study.

In another study by Schermuly *et al.*, co-aerosolization of PDE-inhibitors with iloprost, the stable analogue of PGI₂, caused a doubling of the immediate pulmonary vasodilator response, without suppression of systemic arterial pressure in a rabbit model of PH.²³ The authors recommended the co-nebulization of non-selective PDE-inhibitors with inhaled prostanoids to induce an enhancement and prolongation of the lung vasorelaxant response. These recommendations are supported by the clinical findings of Haraldsson *et al.*, who demonstrated that inhaled milrinone potentiated and prolonged the pulmonary selective vasodilatory effect of inhaled PGI₂ in patients with PH following cardiac surgery.¹²

In contrast to the treatment of PH or right ventricular failure in the postoperative period following cardiac surgery or transplantation, the aim of evaluating the pulmonary hemodynamics of heart transplant candidates is to obtain information about the responsiveness of pulmonary vasculature to vasodilator therapy. Therefore, the optimal screening drug should be highly pulmonary-selective, effective in all patients, easy to administer, short-acting, and without systemic side effects.

In summary, in the evaluation of a limited number of heart transplant candidates, inhaled aerosolized milrinone (2 mg) induced transient selective pulmonary vasodilation which was not accompanied by a decrease of MAP or SVR. Alone, as in our patients with moderate PH, or in combination with prostanoids for patients with higher degrees of PH, milrinone may represent a safe and advantageous inhalation therapy for testing the responsiveness of the pulmonary vasculature prior to cardiac transplantation. We believe that our results justify larger randomized studies to evaluate and to compare the effects of inhaled milrinone with other inhaled vasodilators (e.g., iloprost, NO) in the peri- and postoperative course of patients undergoing heart transplantation.

References

- 1 Kirklin JK, Naftel DC, Kirklin JW, Blackstone EH, White-Williams C, Bourge RC. Pulmonary vascular resistance and the risk of heart transplantation. *J Heart Transplant* 1988; 7: 331–6.
- 2 Erickson KW, Costanzo-Nordin MR, O'Sullivan EJ, *et al.* Influence of preoperative transpulmonary gradient on late mortality after orthotopic heart transplantation. *J Heart Transplant* 1990; 9: 526–37.
- 3 Murali S, Uretsky BF, Reddy PS, Tokarczyk TR, Betschart AR. Reversibility of pulmonary hypertension in congestive heart failure patients evaluated for cardiac transplantation: comparative effects of various pharmacologic agents. *Am Heart J* 1991; 122: 1375–81.
- 4 Kieler-Jensen N, Milocco I, Ricksten SE. Pulmonary vasodilation after heart transplantation. A comparison among prostacyclin, sodium nitroprusside, and nitroglycerin on right ventricular function and pulmonary selectivity. *J Heart Lung Transplant* 1993; 12: 179–84.
- 5 Pepke-Zaba J, Higenbottam TW, Dinh-Xuan A, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. *Lancet* 1991; 338: 1173–4.
- 6 Haraldsson A, Kieler-Jensen N, Nathorst-Westfelt U, Bergh CH, Ricksten SE. Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. *Chest* 1998; 114: 780–6.
- 7 Sablutzki A, Czeslick E, Schubert S, *et al.* Iloprost improves hemodynamics in patients with severe chronic cardiac failure and secondary pulmonary hypertension. *Can J Anesth* 2002; 49: 1076–80.
- 8 Sablutzki A, Czeslick E, Gruenig E, *et al.* First experiences with the stable prostacyclin analog iloprost in the evaluation of heart transplant candidates with increased pulmonary vascular resistance. *J Thorac Cardiovasc Surg* 2003; 125: 960–2.
- 9 Foubert L, Fleming B, Latimer R, *et al.* Safety guidelines for use of nitric oxide (Letter). *Lancet* 1992; 339: 1615–6.
- 10 Miller OI. Rebound pulmonary hypertension on withdrawal from inhaled nitric oxide (Letter). *Lancet* 1995; 346: 51–2.
- 11 Olschewski H, Walrmath D, Schermuly R, Ghofrani HA, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996; 124: 820–4.
- 12 Haraldsson A, Kieler-Jensen N, Ricksten SE. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. *Anesth Analg* 2001; 93: 1439–45.
- 13 Pamboukian SV, Carere RG, Webb JG, *et al.* The use of milrinone in pre-transplant assessment of patients with congestive heart failure and pulmonary hypertension. *J Heart Lung Transplant* 1999; 18: 367–71.
- 14 McGoon M, Guterman D, Steen V, *et al.* Screening, early detection, and diagnosis of pulmonary arterial hypertension. ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: 14S–34S.
- 15 Wiesenack C, Fiegl C, Keyser A, Laule S, Prasser C, Keyl C. Continuously assessed right ventricular end-diastolic volume as a marker of cardiac preload and fluid respon-

- siveness in mechanically ventilated cardiac surgical patients. *Crit Care* 2005; 9: R226–33.
- 16 Sakka SG, Rubl CC, Pfeiffer UJ, et al. Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. *Intensive Care Med* 2000; 26: 180–7.
 - 17 Jaski BE, Fifer MA, Wright RF, et al. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure. Dose-response relationships and comparison to nitroprusside. *J Clin Invest* 1985; 75: 643–9.
 - 18 Feneck RO. Effects of variable dose milrinone in patients with low cardiac output after cardiac surgery. *Am Heart J* 1991; 121: 1995–9.
 - 19 Trochu JN. Pulmonary hypertension and cardiac transplantation (French). *Arch Mal Coeur Vaiss* 2004; 97: 53–60.
 - 20 Sablotzki A, Hentschel T, Gruenig E, et al. Hemodynamic effects of inhaled aerosolized iloprost and inhaled nitric oxide in heart transplant candidates with elevated pulmonary vascular resistance. *Eur J Cardiothorac Surg* 2002; 22: 746–52.
 - 21 Bocchi EA, Bacal F, Auler jr JO, et al. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. *Am J Cardiol* 1994; 74: 70–2.
 - 22 Gessler T, Schmebl T, Hoeper MM, et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. *Eur Respir J* 2001; 17: 14–9.
 - 23 Schermuly RT, Krupnik E, Tenor H, et al. Coaerosolization of phosphodiesterase inhibitors markedly enhances the pulmonary vasodilatory response to inhaled iloprost in experimental pulmonary hypertension. *Am J Respir Crit Care Med* 2001; 164: 1694–700.