Journal of Clinical Anesthesia (2006) **18**, 108–113

ELSEVIER

Journal of Clinical Anesthesia

Original contribution

Inhaled aerosolized iloprost in the evaluation of heart transplant candidates—experiences with 45 cases

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Received 7 October 2004; accepted 11 August 2005

Keywords:
Heart transplantation;
Iloprost inhalation;
Pulmonary hemodynamics

Abstract

Purpose: Pulmonary hypertension represents a significant predictor of postoperative right heart insufficiency and increased mortality in patients undergoing orthotopic heart transplantation. As the use of intravenous vasodilators is limited by their systemic effects, we evaluated the pulmonary and systemic hemodynamic effects of inhaled aerosolized iloprost in heart transplant candidates with elevated pulmonary vascular resistance.

Methods: Forty-five male heart transplant candidates with dilated or ischemic cardiomyopathy were included in the study. After assessing baseline hemodynamics, 20 μg of aerosolized iloprost was administered by ultrasonic inhalation. All patients were breathing spontaneously.

Results: Inhalation of iloprost reduced pulmonary vascular resistance index (395 $\pm$ 205 vs 327 $\pm$ 222 dyne $\cdot$ s $\cdot$ cm^{-5} $\cdot$ m^{-2}; $P < 0.05$) and mean pulmonary arterial pressure (28.7 $\pm$ 10 vs 24.3 $\pm$ 10 mm Hg; $P < 0.05$). An additional improvement of ventricular performance with an increase of cardiac index (2.7 $\pm$ 0.7 vs 3.0 $\pm$ 0.8 L $\cdot$ min^{-1} $\cdot$ m^{-2}; $P < 0.05$) and a decrease of pulmonary capillary wedge pressure (16.6 $\pm$ 7.7 vs 13.4 $\pm$ 7.3 mm Hg; $P < 0.05$) was accompanied by a slight decrease of systemic vascular resistance (1280 $\pm$ 396 vs 1172 $\pm$ 380 dyne $\cdot$ s $\cdot$ cm^{-5}; $P < 0.05$). However, the mean arterial pressure remained uninfluenced.

Conclusions: Inhaled aerosolized iloprost effectively reduces mean pulmonary arterial pressure and also induces an increase in cardiac index. Further advantages of iloprost inhalation are the lack of adverse reactions and ease of administration. Iloprost represents a useful drug to screen for vascular reactivity in cardiac transplantation patients.

1. Introduction

Pulmonary hypertension and increased pulmonary vascular resistance (PVR) after orthotopic heart transplantation significantly contribute to right ventricular failure

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doi:10.1016/j.jclinane.2005.08.018

and increase perioperative morbidity and mortality [1,2]. Therefore, measurement of pulmonary hemodynamics is a routine procedure in the assessment of potential transplantation recipients [3]. Information on the reversibility of pulmonary hypertension in response to vasodilator therapy is of great interest for the postoperative management of right heart failure. Usual therapeutic management has consisted of intravenous vasodilators such as nitrates, sodium nitroprusside, or prostanoids, but lack of selectivity for the pulmonary vasculature and associated systemic hypotension with increasing dosage represents a strong limiting factor [4].

Administration of vasodilators by inhalation seems to be an advantageous concept because large concentrations can be selectively presented to the pulmonary circulation. Inhaled nitric oxide and prostacyclin (PGI_2) have been shown to act as selective pulmonary vasodilators without systemic effects in patients with primary and secondary pulmonary hypertension as well [5,6]. Unfortunately, nitric oxide is a toxic molecule and requires specialized delivery systems and monitoring due to the production of methemoglobin and higher oxides of nitrogen [7]. Because of its short half-life, nitric oxide has to be administered continuously, and even brief interruptions may cause a dangerous rebound of pulmonary hypertension [8]. The advantages of inhaled prostacyclin include the lack of toxic reactions and ease of administration. On the other hand, Haraldsson et al [6] found no improved effects on hemodynamic variables, comparing inhaled prostacyclin with inhaled nitric oxide in the evaluation of heart transplant candidates.

Olschewski et al [9] described the use of aerosolized iloprost, a carbacyclin analogue of PGI_2, for severe pulmonary hypertension. Iloprost has a plasma half-life of 20 to 30 minutes. When inhaled, it induces selective pulmonary vasodilation that persists for about 2 to 4 hours. In contrast to nitric oxide, inhaled iloprost may also exert systemic circulatory effects, as the molecule will not be rapidly inactivated in the pulmonary vascular bed and "spillover" in the systemic circulation. In patients with primary pulmonary hypertension, iloprost was more potent than inhaled nitric oxide [10].

In own previous studies, we could show that inhaled aerosolized iloprost improves hemodynamics in patients with chronic cardiac failure [11] and was more potent concerning the reduction of mean pulmonary arterial pressure (MPAP) and PVR in heart transplant candidates with secondary pulmonary hypertension compared with inhaled nitric oxide [12]. The reduction of pulmonary hypertension was not accompanied by systemic effects or hypotension. However, our study had several limitations, which have been obstacles to a general recommendation for the use of iloprost in the evaluation of heart transplant candidates: the limited number of investigated patients (n = 20) and the fact that a jet nebulizer (Cirrus-Nebulizer, Germany) with a limited output and limited efficiency was used.

The aim of our study was to verify the results of the preceding investigation with a better inhalation device (ultrasonic nebulizer) in a large number of patients (n = 45).

2. Patients and methods

The study was designed as a single-center, prospective, nonrandomized, open clinical study. It was not supported by any industrial grant. The protocol was approved by the Human Ethics Committee of the Medical Faculty, University of Halle-Wittenberg. Forty-five consecutive male patients scheduled for diagnostic right heart catheterization were included in the study after informed consent. The diagnoses were ischemic (n = 19) or dilated (n = 26) cardiomyopathy. Patients received their usual regimen of oral medication in the morning; no additional sedation was given during insertion of lines or the study procedure. During the whole study period, all patients were breathing spontaneously via a mouthpiece connected to the nebulizer (Fig. 1). Patients were informed to breathe slowly and to take vital capacity breaths during the inhalation period.

For inhalation of aerosolized iloprost, an ultrasonic nebulizer (Opti-Neb, Nebu-tec GmbH, Elsenfeld, Germany) was used; the nebulized particle size ranges from 3 to 5 μm. Twenty micrograms of iloprost was diluted in 3 mL of 0.9% sodium chloride and inhaled completely within 15 minutes.

Measurements of hemodynamics were performed using a radial artery catheter (PICCO, Pulsion GmbH) and a pulmonary artery catheter (model CCO-V-CCO/CEDV/177F75, Edwards Lifesciences, Irvine, CA, USA), inserted via the left 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 arterial pressure; central venous pressure (CVP); pulmonary capillary wedge pressure

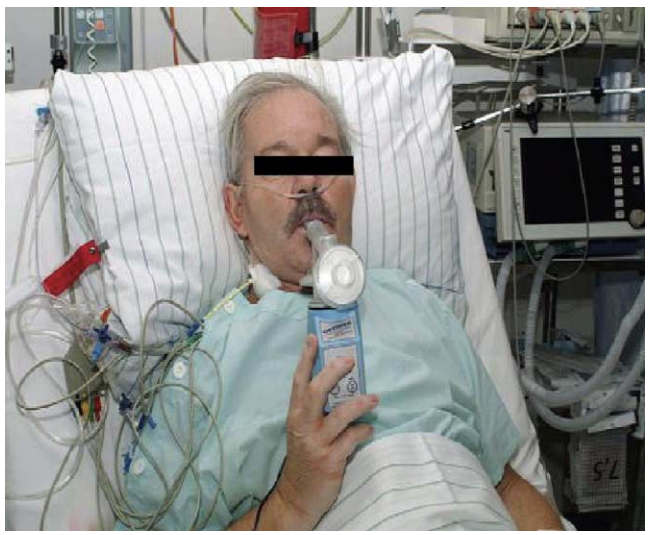

Fig. 1 Iloprost-inhalation by ultrasonic nebulization.

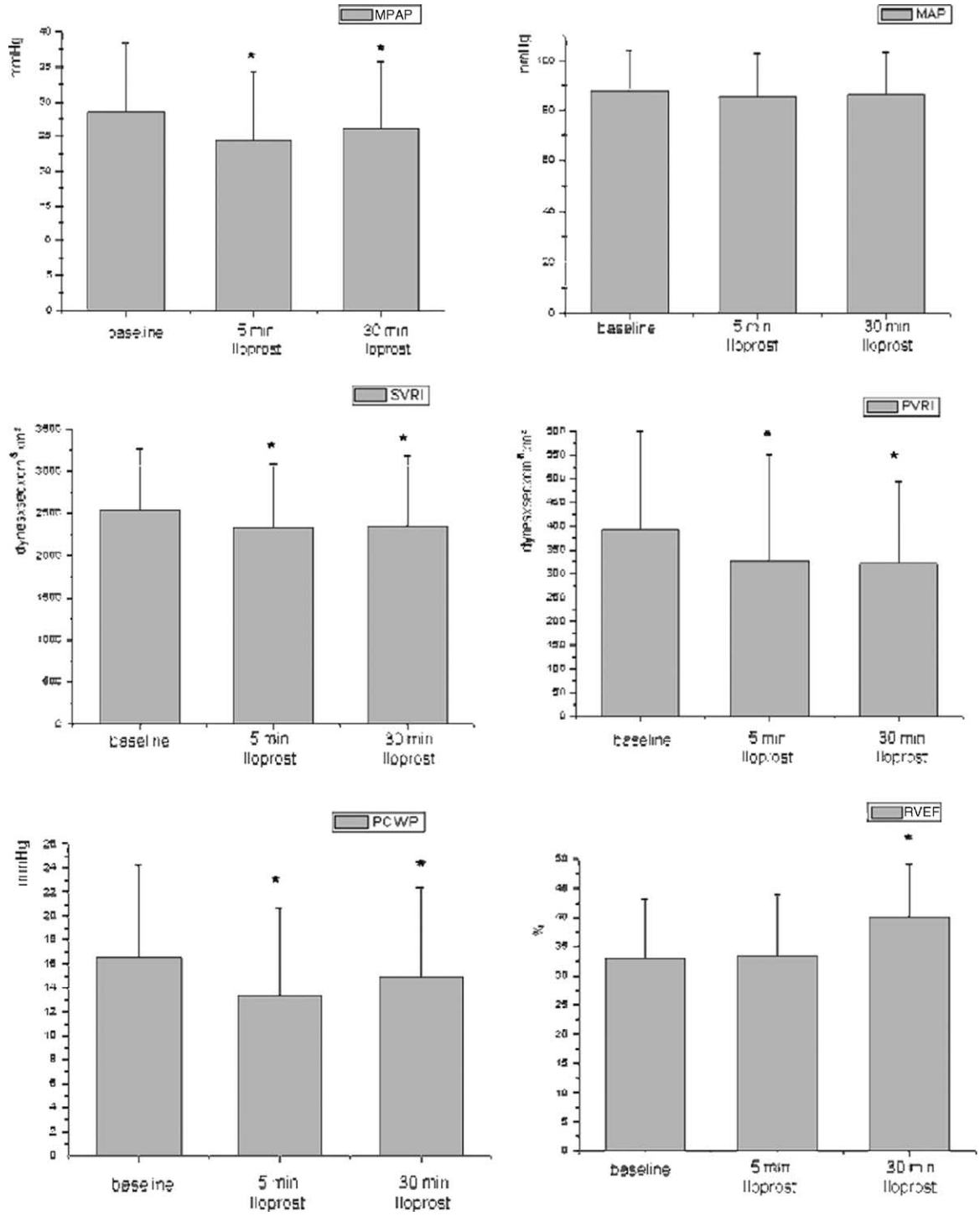

Fig. 2 Effect of iloprost inhalation on MPAP, MAP, SVRI and PVRI, PCWP, and RVEF. *$P < 0.05$ compared with baseline.

(PCWP); systemic vascular resistance (SVR); and PVR. Cardiac output was measured; cardiac index (CI), PVR and SVR indices (PVRI and SVRI), right ventricular ejection fraction (RVEF), intrathoracal blood volume (ITBV), and extravascular lung water (EVLW) were calculated.

The methodology of RVEF measurement uses the saved electrocardiograph signal and generates a relaxation waveform that resembles the bolus thermodilution washout decay curve. Calculation of RVEF is based on estimation of the exponential decay time constant (τ) of this curve and HR: RVEF = 1 − exp (−60/ [τ × HR]) [13]. Single thermodilution ITBV and EVLW were calculated according to the formula described by Sakka et al [14]: ITBV = (1.25 · GEDV) − 28.4 (mL) and EVLW = ITTV − ITBV (mL) (GEDV indicates global end-diastolic volume; ITTV, intrathoracic thermal volume).

Table 1 Influence of inhaled iloprost on systemic and pulmonary hemodynamics

Parameter	Baseline	5 min after iloprost inhalation	30 min after iloprost inhalation	*P*
HR (1/min)	80.7 ± 17.3	80.4 ± 14.6	80.8 ± 17.2	NS
CI (L · min^{-1} · m^{-2} BSA)	2.7 ± 0.7	2.9 ± 0.7*	3.0 ± 0.8*	<0.05
MAP (mm Hg)	87.8 ± 16.6	85.5 ± 17.8	86.4 ± 17.3	NS
MPAP (mm Hg)	28.7 ± 10	24.3 ± 10*	26.1 ± 10*	<0.05
SVRI (dyne · s · cm^{-5} · m^{-2})	2542 ± 730	2333 ± 747*	2349 ± 831*	<0.05
SVR (dyne · s · cm^{-5})	1283 ± 396	1172 ± 380*	1180 ± 417*	<0.05
PVRI (dyne · s · cm^{-5} · m^{-2})	394 ± 205	327 ± 222*	323 ± 170*	<0.05
PVR (dyne · s · cm^{-5})	202 ± 117	167 ± 118*	163 ± 89*	<0.05
PCWP (mm Hg)	16.6 ± 7.7	13.4 ± 7.3*	14.9 ± 7.5*	<0.05
TPG (mm Hg)	12.1 ± 4.8	10.8 ± 6.4	11.2 ± 5	NS
RVEF (%)	33.1 ± 10	33.4 ± 10.7	40.2 ± 8.9*	<0.05
ITBV (mL)	2071 ± 568	2088 ± 653	1970 ± 515	NS
EVLW (mL)	939 ± 495	925 ± 331	989 ± 544	NS

Data are expressed as mean ± SD.
* $P < 0.05$ vs baseline (n = 45).

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

3. Statistics

Statistical analysis was made by an independent bureau of statistics (MoRe.data, Giessen, Kerkrader Strasse, Germany). The data are presented as mean ± SD. After testing for normal distribution with the Shapiro-Wilk test, comparison of data was made by nonparametric Wilcoxon test with Bonferroni correction. A P value less than 0.05 was considered to indicate statistical significance.

4. Results

We studied 45 adult male patients. The mean age was 49 ± 9 years; the body surface area was 2.00 ± 0.2 m^2. Except one patient who developed a mild flush, all treated patients tolerated iloprost inhalation without side effects.

The effects of iloprost on pulmonary and systemic hemodynamics are presented in Fig. 2 and Table 1: 5 and 30 minutes after inhalation of iloprost, there were no significant changes regarding HR, MAP, transpulmonary gradient (TPG), EVLW, and ITBV compared with the baseline measurement.

In contrast to MAP, we found a slight but significant decrease of SVR 5 (1172 ± 380 vs 1283 ± 396 dyne · s · cm^{-5}; $P < 0.05$) and 30 minutes (1180 ± 417 vs 1283 ± 396 dyne · s · cm^{-5}; $P < 0.05$) after administration of iloprost. Mean pulmonary arterial pressure (24.3 ± 10 after 5 minutes and 26.1 ± 10 after 30 minutes vs 28.7 ± 10 mm Hg; $P < 0.05$) and PCWP (13.4 ± 7.3 after 5 minutes and 14.9 ± 7.5 after 30 minutes vs 16.6 ± 7.7 mm Hg; $P < 0.05$) were both significantly reduced because the TPG remained uninfluenced. Cardiac index was significantly increased 5 (2.9 ± 0.7 vs 2.7 ± 0.7 L · min^{-1} · m^{-2} BSA; $P < 0.05$) and 30 minutes (3.0 ± 0.8 vs 2.7 ± 0.7 L · min^{-1} · m^{-2} BSA; $P < 0.05$) after iloprost administration. Pulmonary vascular resistance (167 ± 118 after 5 minutes and 163 ± 89 after 30 minutes vs 202 ± 117 dyne · s · cm^{-5}; $P < 0.05$) and PVRI (327 ± 222 after 5 minutes and 323 ± 170 after 30 minutes vs 394 ± 205 dyne · s · cm^{-5} · m^{-2}; $P < 0.05$) were significantly reduced by iloprost. The reduction of PVR was followed by a significant increase in RVEF 30 minutes after iloprost (40.2% ± 8.9% vs 33.1% ± 10%; $P < 0.05$).

5. Discussion

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

In the last years, several inhalation drugs could be established for evaluation of heart transplant candidates with and without accompanying pulmonary hypertension [6,11,12]. In own previous investigations, we could show that iloprost, the longer-acting analogue of prostacyclin, represents an attractive alternative to the inhalation of nitric oxide. Iloprost as a pulmonary selective vasodilator has several advantages compared with nitric oxide, most important were the lack of adverse reactions and the ease of administration [12,15]. The disadvantage of the study design was the use of a jet nebulizer: the limited output of this device required a long inhalation period and a high dosage of iloprost (50 μg).

As described by Gessler et al [16], the total output of an ultrasonic nebulizer is approximately 2.5 to 2.7 times higher than that of the jet nebulizer. Even more pronounced is the difference with regard to the output at the mouthpiece: this parameter, describing the amount of aerosol delivered to the patient, is more than 6 times higher in ultrasonic nebulizer systems [16]. With our results, we can confirm the data of Gessler et al [16]: 20 μg of iloprost, administered by ultrasonic nebulization, induced a maximum MPAP reduction of 15.6 %; the administration of 50 μg iloprost by jet nebulization in our previous study induced a reduction of 16.4% [12]. The markedly higher efficiency and output of the ultrasonic device in the present study induced a significant spillover of the substance, leading to a significant decrease of SVR that was not accompanied by a drop of MAP. The consequences of SVR reduction were an increase of CI and a decrease of PCWP.

The improvement of left heart function may be induced by systemic vasodilation in response to iloprost inhalation. Another explanation may be a direct positive inotropic effect of iloprost, mediated by an increase of cAMP in cardiomyocytes [17]. In an experimental model, Kisch-Wedel et al [18] could show that intravenously administered iloprost (8 μg/kg per minute) induced a significant increase of left ventricular myocardial contractility.

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 after inhalation of nitric oxide [19]. In this context, the moderate reduction of SVR and PCWP induced by iloprost may prevent this dangerous increase in left ventricular filling pressure and can be interpreted as a beneficial "side effect" of iloprost inhalation. This interpretation is supported by the fact that ITBV and EVLW remained uninfluenced after inhalation of iloprost in our study.

Langer et al [20] reported a case of progressive right ventricular failure in the early postoperative period after orthotopic heart transplantation, which was successfully treated by inhalation of iloprost. Nebulization of aerosolized iloprost resulted in a reduction of PVR (−26%) and an increase of CI (24%), whereas no effect on MAP was observed [20]. These findings are in agreement with the results of our study and may justify the use of iloprost in the perioperative management of pulmonary hypertension in patients with heart transplantation.

Nevertheless, the "ideal" dosage of iloprost is still unknown and under discussion. Reflecting the fact that the effectiveness of inhaled aerosolized drugs depends on the nebulizer system, the chemical characteristics of the drug, the kind of underlying disease, and the individual anatomical characteristics of the bronchial system. The ideal dosage will always be an "individual" dosage. In an actual review, Czeslick et al [21] recommend a dosage of 5 to 20 μg for an ultrasonic device.

In summary, we can show again that inhaled aerosolized iloprost induces a reliable hemodynamic response in the evaluation of heart transplant candidates with elevated pulmonary resistance. Therefore, we recommend the use of iloprost as a routine screening drug for pulmonary vascular reactivity. We also recommend further large comparative studies to evaluate the place of iloprost in the management of severe pulmonary hypertension in cardiac transplantation.

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