Cardiothoracic Anesthesia, Respiration and Airway

Iloprost improves hemodynamics in patients with severe chronic cardiac failure and secondary pulmonary hypertension

[L'iloprost améliore l'hémodynamique chez des malades souffrant d'insuffisance cardiaque chronique et d'hypertension artérielle pulmonaire]

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Purpose: Significant pulmonary hypertension is a predictor of post-operative right heart insufficiency and increased mortality in patients undergoing orthotopic heart transplantation. Since the use of iv vasodilators is limited by their systemic effects, we evaluated the pulmonary and systemic hemodynamic effects of inhaled aerosolized iloprost (IP) in heart transplant candidates with elevated pulmonary vascular resistance (PVR).

Methods: Twenty-nine male heart transplant candidates because of dilated or ischemic cardiomyopathy with elevated PVR were included in the study. After assessing baseline hemodynamics, 50 µg aerosolized IP were administered by inhalation.

Results: Inhalation of iloprost reduced PVR index (PVRI; 416 ± 180 vs 349 ± 173 dyn·sec⁻¹·m⁻²·cm⁻⁵; $P < 0.01$) and mean pulmonary artery pressure (MPAP; 28.6 ± 9 vs 24.2 ± 9.1 mmHg; $P < 0.01$), but did not affect blood pressure or systemic vascular resistance. An additional improvement of ventricular performance with an increase of cardiac index (CI; 2.8 ± 0.7 vs 2.6 ± 0.7 L·min⁻¹·m⁻²; $P < 0.05$) and a decrease of pulmonary capillary wedge pressure (PCWP; 15.6 ± 6.8 vs 12.8 ± 7.1 mmHg; $P < 0.01$) was observed after inhalation of IP.

Conclusions: Inhaled aerosolized iloprost effectively reduces MPAP and is accompanied by an increase in CI and stroke index. Further advantages of iloprost inhalation are the lack of adverse reactions and ease of administration. Iloprost may be a useful drug to screen for vascular reactivity in cardiac transplantation patients.

Objectif : L'hypertension artérielle pulmonaire élevée est un prédicteur d'insuffisance postopératoire du cœur droit et elle accroît la mortalité des candidats à la transplantation cardiaque. L'usage des vasodilatateurs iv étant limité par leurs effets généraux, nous avons évalué les effets pulmonaires et généraux de l'iloprost (IP) en inhalation aérosol chez des candidats à la transplantation cardiaque présentant une résistance vasculaire pulmonaire élevée (RVP).

Méthode : Vingt-neuf hommes, candidats à une transplantation cardiaque à cause d'une cardiomyopathie dilatée ou ischémique et d'une RVP élevée, ont participé à l'étude. À la suite de l'évaluation hémodynamique de base, 50 µg d'IP en aérosol ont été administrés par inhalation.

Résultats : L'inhalation d'iloprost a réduit l'index de RVP (IRVP; 416 ± 180 vs 349 ± 173 dyn·sec⁻¹·m⁻²·cm⁻⁵; $P < 0.01$) et la pression artérielle pulmonaire moyenne (PAPM; $28,6 \pm 9$ vs $24,2 \pm 9,1$ mmHg; $P < 0.01$), mais n'a pas affecté la tension artérielle ou la résistance vasculaire générale. Une amélioration supplémentaire de la performance ventriculaire accompagnée d'une hausse de l'index cardiaque (IC; $2,8 \pm 0,7$ vs $2,6 \pm 0,7$ L·min⁻¹·m⁻²; $P < 0.05$) ainsi qu'une baisse de la pression capillaire pulmonaire bloquée (PCPB; $15,6 \pm 6,8$ vs $12,8 \pm 7,1$ mmHg; $P < 0.01$) ont été observées après l'inhalation d'IP.

Conclusion : L'iloprost en aérosol administré par inhalation réduit efficacement la PAPM. Cet effet est accompagné d'une hausse de l'IC et de l'index systolique. Les autres avantages de l'inhalation d'iloprost sont l'absence de réactions indésirables et la facilité d'administration. L'iloprost pourrait servir au dépistage de la réactivité vasculaire chez les candidats à la transplantation cardiaque.

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AN elevated pulmonary vascular resistance (PVR) or transpulmonary gradient (TPG) significantly contributes to postoperative right heart insufficiency and increased perioperative mortality following orthotopic heart transplantation.^{1,2} Information on the reversibility of elevated pulmonary hypertension in response to vasodilator therapy is of great interest 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 case of elevated PVR, drugs such as nitrates, sodium nitroprusside, or prostacyclin are used to determine whether the abnormalities of the pulmonary vascular bed are reversible or not.

The therapeutic limitation of *iv* vasodilators is the accompanying systemic hypotension.⁴ Inhaled nitric oxide (NO) and prostacyclin (PGI₂) have been shown to act as selective pulmonary vasodilators without systemic effects in patients with primary and secondary pulmonary hypertension 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 pulmonary hypertension.¹⁰ The advantages of inhaled prostacyclin include the lack of toxic reactions and ease of administration. On the other hand, Haraldsson found no advantage of inhaled prostacyclin over NO in the evaluation of heart transplant (HTx) candidates.⁸

Olschewski and coworkers described the use of aerosolized iloprost, a carbacyclin analogue of PGI₂, for severe pulmonary hypertension.¹¹ Iloprost has a plasma half-life of 20 to 30 min. When inhaled it induces pulmonary vasodilation that persists for about two to four hours. In contrast to NO, inhaled iloprost may also exert systemic circulatory effects, as the molecule will not be rapidly inactivated in the pulmonary vascular bed and "spill over" in the systemic circulation.⁸ In patients with primary pulmonary hypertension iloprost was more potent than inhaled NO.¹²

Currently, there is little information on the use of iloprost in patients with pulmonary hypertension secondary to chronic cardiac failure. Langer *et al.* reported a case of successful treatment of right heart insufficiency after heart transplantation by the inhalation of iloprost.¹³ The aim of the present study was to investigate the hemodynamic effects of inhaled aerosolized iloprost in HTx candidates with pulmonary hypertension.

Materials and methods

The study protocol was approved by the Human Ethics Committee of the Faculty of Medicine, University of Halle/Wittenberg. Thirty consecutive male patients with elevated PVR (206 ± 94 dyn·sec⁻¹·cm⁻⁵) scheduled for diagnostic right heart catheterization were included after giving informed consent. In one patient the evaluation was not performed due to an infection of the upper respiratory tract. All patients were candidates for cardiac transplantation and the only contraindication to evaluation was acute cardiac failure with lung edema. The diagnoses included ischemic ($n = 16$) or dilated ($n = 13$) cardiomyopathy. Patients received their usual regimen of oral medication in the morning. No additional sedation was administered during the insertion of central lines or the study procedure.

Measurement of hemodynamics was performed using a radial artery catheter and a pulmonary artery catheter (Edwards model 93A-434-7.5F; Baxter Healthcare Corp., Irvine, California, USA), inserted via the left jugular vein. The following variables were measured or calculated: Mean arterial blood pressure (MAP), heart rate (HR), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), stroke volume (SV), systemic (SVR) and PVR. Cardiac output (CO) was measured, cardiac index (CI), pulmonary and systemic vascular resistance indices (PVRI, SVRI), and stroke index (SI) were calculated. All variables were measured at baseline and at the end of each evaluation period. Triplicate measurements were averaged for each reported CO.

Prior to the acquisition of baseline measurements and during the whole study period the patients were breathing medical air and oxygen in an inspiratory concentration of 25% via a tight-fitting face mask using a non-rebreathing circuit in an assistant-spontaneous-breathing (ASB) mode (Ventilator EVITA-IV; Drägerwerk, Lübeck, Germany). 50 µg of iloprost were diluted in 3 mL of isotonic saline solution and nebulized (Cirrus-Nebulizer; Germany) for 15 min. Another hemodynamic measurement followed five minutes after the iloprost inhalation. After the end of evaluation the patients stayed for another six hours in the intensive care unit (ICU). Before the removal of the pulmonary artery catheter and transfer to the general ward, arterial blood pressure, blood gas analysis, and pulmonary artery pressure were measured to document that the patients' condition had not worsened.

Statistics

Statistical analysis was made by an independent bureau of statistics (MoRe.Data, Giessen, Germany). The

TABLE I Biometric data of patients

	<i>n</i>	<i>Mean ± SD</i>	<i>Median (range)</i>
Age (yr)	29	51.4 ± 7.1	52 (11)
Weight (kg)	29	173.2 ± 7.4	174 (8.5)
Height (cm)	29	82.5 ± 13.6	84 (13)
BSA (m ²)	29	2.0 ± 0.2	2.1 (0.1)

Data are presented as mean ± SD, and median; *n* = 29; BSA = body surface area.

data are presented as mean values and standard deviation (SD). Comparison of data was with the non-parametric Wilcoxon-test. A *P*-value < 0.05 was considered to indicate statistical significance.¹⁴

Results

Mean age was 51.4 ± 7.1 yr, and body surface area was 2.02 ± 0.2 m² (Table I). All patients tolerated iloprost-inhalation without side effects like cough or flush.

The hemodynamic effects of inhaled iloprost are illustrated in Table II. There were no significant effects on MAP, HR, and systemic vascular resistance or systemic vascular resistance index compared to baseline.

Iloprost-inhalation resulted in a significant decrease of MPAP (24.2 ± 9.1 *vs* 28.6 ± 9 mmHg, *P* < 0.01) and PVR (174 ± 89 *vs* 206 ± 94 dyn·sec⁻¹·cm⁻⁵, *P* < 0.05) or PVRI (349 ± 173 *vs* 416 ± 183 dyn·sec⁻¹·m⁻²·cm⁻⁵, *P* < 0.01). In addition to the effects on the pulmonary vascular bed we found an improvement of ventricular function in patients treated with iloprost: CI (2.8 ± 0.7 *vs* 2.4 ± 0.6 L·min⁻¹·m², *P* < 0.05) and SI (35.4 ± 9.8 *vs* 32.5 ± 9.4 mL·m², *P* < 0.01) increased after iloprost-inhalation. The PCWP was reduced by iloprost (12.8 ± 7.1 *vs* 15.6 ± 6.8 mmHg, *P* < 0.01).

Discussion

In our study, we studied the effects of inhaled aerosolized iloprost in patients with pulmonary hypertension due to chronic cardiac failure. Iloprost caused a significant reduction in MPAP and PVR. The SVR and arterial blood pressure were not affected. In addition to the beneficial effects on the pulmonary vascular bed, iloprost caused a significant increase of CI and SI. Side effects like cough or flush were not observed in our patients.

The use of NO and/or aerosolized PGI₂ for the evaluation of HTx candidates with pulmonary hypertension has been described previously.^{8,15,16} The benefits of iloprost in these patients remain unclear. All studies could show a selective pulmonary vasodilation with reduced pulmonary arterial pressure and an

improved oxygenation. Inhaled NO in concentrations ranging from 5 to 80 ppm have been shown to reduce PVR in patients after heart transplantation,¹⁷ cardiac surgical patients,¹⁸ acute respiratory distress syndrome,¹⁹ and chronic pulmonary hypertension.²⁰ Haraldsson and coworkers described a selective dose-dependent decrease in PVR and TPG at an inhaled concentration of 10 µg PGI₂ with no effects on systemic circulation.²¹ The effects of PGI₂ and inhaled NO on the induction of pulmonary vasodilation in HTx candidates were comparable. Advantages of the prostacyclin-therapy were the lack of adverse events and ease of administration.⁸

Hoepfer and coworkers described more potent effects of iloprost on the pulmonary vascular bed in patients with primary pulmonary hypertension when compared to inhaled NO.¹² In comparison to the results of Hoepfer we found similar effects of iloprost in our patients with secondary pulmonary hypertension: The reduction of pulmonary arterial pressure was accompanied by an increase of CO and SI. The improvement of cardiac function may be induced by a degree of systemic vasodilation in response to iloprost, but we found no reduction of MAP or SVR compared to the baseline. Direct positive inotropic effects of prostanooids are documented in experimental studies with rat cardiomyocytes,²² but it remains unclear if these findings are clinically significant.

Erickson and colleagues compared TPG, pulmonary arterial systolic pressure, pulmonary vascular resistance, and pulmonary vascular resistance index, to identify which variable most accurately predicts poor outcome after orthotopic heart transplantation.² They found that only TPG predicted survival in these patients: six- and 12-month mortality after heart transplantation in patients with preoperative TPG < 12 mmHg was 5%, mortality of recipients with preoperative TPG ≥ 12 mmHg was 24% (six months, *P* = 0.003) and 36% (12 months, *P* = 0.0005). In contrast to other authors, who found an increase of PCWP during pulmonary vasodilation with NO,²³ we could document a significant reduction of PCWP during iloprost-inhalation. Because of this, the resulting reduction of TPG was not significant. Thus, it appears that it may be necessary to evaluate hemodynamic variables other than the TPG alone to reach a decision.

The hemodynamic effects of inhaled aerosolized iloprost are in agreement with the documented effects of *iv* PGI₂.¹¹ However, *iv* prostacyclin administration is often limited by its effects on arterial blood pressure in patients with chronic heart failure.²⁴ This systemic hypotension limits the use of *iv* nonselective vasodilators in the evaluation of heart failure patients, espe-

TABLE II

Variables	Baseline		Iloprost		P value
	Mean $\pm$ SD	Median (range)	Mean $\pm$ SD	Median (range)	
HR	82.6 $\pm$ 15.3	81 (22.5)	81 $\pm$ 15.8	79 (21)	NS
CO	5.4 $\pm$ 1.6	5.3 (1.6)	5.6 $\pm$ 1.7	5.4 (2.1)	NS
MAP	91.9 $\pm$ 15.9	90 (20)	91.2 $\pm$ 15.9	88 (20.5)	NS
PAPm	28.6 $\pm$ 9	29 (15)	24.2 $\pm$ 9.1**	22 (12)	P < 0.01
PCWP	15.6 $\pm$ 6.8	13 (10.5)	12.8 $\pm$ 7.1**	11 (11)	P < 0.01
CVP	7.1 $\pm$ 3.3	6 (3)	6.6 $\pm$ 4.7	6 (5)	NS
SVR	1345.6 $\pm$ 399.1	1227 (683.5)	1294.1 $\pm$ 352.4	1248 (582.5)	NS
TPG	13 $\pm$ 4.9	11 (6)	11.9 $\pm$ 6.7	10 (8.5)	NS
PVR	206.4 $\pm$ 93.9	170 (162)	174.4 $\pm$ 89.3*	165 (117)	P < 0.05
CI	2.6 $\pm$ 0.7	2.5 (0.8)	2.8 $\pm$ 0.7*	2.6 (0.6)	P < 0.05
SI	32.5 $\pm$ 9.4	31.9 (14)	35.4 $\pm$ 9.8**	35.8 (11.3)	P < 0.01
SVRI	2687.4 $\pm$ 781.9	2655 (1317.5)	2598.6 $\pm$ 735	2499 (1062)	NS
PVRI	416.5 $\pm$ 183	379 (209)	349.2 $\pm$ 172.8**	319 (239)	P < 0.01

Influence of inhaled iloprost on heart rate (HR; units min⁻¹), cardiac output (CO; units: L·min⁻¹), mean arterial blood pressure (MAP; units mmHg), mean pulmonary arterial pressure (MPAP; units mmHg), pulmonal capillary wedge pressure (PCWP; units: mmHg), central venous pressure (CVP; units: mmHg), systemic vascular resistance (SVR; units: dyn·sec·cm⁻⁵), pulmonary vascular resistance (PVR; units: dyn·sec⁻¹·cm⁻⁵), cardiac index (CI; units: L·min⁻¹·m⁻²), stroke index (SI; units mL·m⁻²), SVR-index (SVRI; units: dyn·sec⁻¹·m²·cm⁻⁵), and PVR-index (PVRI; units: dyn·sec⁻¹·m²·cm⁻⁵). Data are expressed as mean $\pm$ SD, and median; *n* = 29; **P* < 0.05; ***P* < 0.01 compared to the baseline.

cially those with ischemic heart disease, and in the postoperative treatment of patients after heart transplantation. In contrast, none of our patients presented decreases of arterial blood pressure or SVR or worsening of cardiac function during inhalation of iloprost.

Langer and coworkers reported a case of right heart failure in the early postoperative period following orthotopic heart transplantation successfully treated with inhalation of iloprost (16 µg, applied six times a day). The iloprost inhalation induced a reduction of PVR (-23.5%), and an increase of CI (24%), while no effect on SVR was observed (-2.8%). The authors recommended iloprost inhalation as an effective alternative to NO in the intensive care management of acute right heart failure after orthotopic heart transplantation.¹³ In another case report, Wittwer *et al.* used an intensified treatment with *iv* prostacyclin and dobutamine combined with iloprost inhalation (100 µg·day⁻¹), to stabilize a transplantation candidate for a waiting period of 21 days.²⁵

The results of our study show that inhaled aerosolized iloprost effectively improved hemodynamics in 29 HTx candidates with elevated PVR. Further potential advantages of iloprost inhalation are the lack of adverse reactions and ease of administration. Based on these results, we recommend comparative studies to evaluate the place of iloprost in the management of perioperative pulmonary hypertension in cardiac transplantation in the near future.

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