Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized, prospective, double-blind study

Khalil Fattouch[a], Fabrizio Sbraga[a], Roberta Sampognaro[a], Giuseppe Bianco[a], Marco Gucciardo[a], Carlo Lavalle[b], Carmine Dario Vizza[b], Francesco Fedele[b] and Giovanni Ruvolo[a]

Objective **Pulmonary hypertension can already be present in patients undergoing cardiac surgery or can be exacerbated by cardiopulmonary bypass. Postoperative treatment is still a challenge for physicians. The aim of this study was to evaluate the effects of inhaled prostacyclin ($iPGI_2$) and nitric oxide (iNO) compared with those of intravenous vasodilators.**

Methods **This prospective, randomized, double-blind study included 58 patients affected by severe mitral valve stenosis and pulmonary hypertension with high pulmonary vascular resistance (> 250 dynes·s·cm^{-5}) and a mean pulmonary artery pressure > 25 mmHg. All patients were monitored by central venous, radial arterial and Swan–Ganz catheters. Data were recorded at six different time points, before induction of anaesthesia, during and after surgery. Prostacyclin and nitric oxide were administered by inhalation 5 min before weaning from cardiopulmonary bypass and continued in the intensive care unit. Right ventricular function was evaluated by transoesophageal echocardiography.**

Results **Hospital mortality was 3.4%. After drug administration, the mean pulmonary artery pressure and pulmonary vascular resistance were significantly decreased in the iNO and $iPGI_2$ groups with respect to the baseline values ($P < 0.05$) and such a decrease was maintained throughout the study; this was not observed in the control group. In the iNO and $iPGI_2$ groups we demonstrated a significant increase in cardiac indices and right ventricular ejection fraction after drug administration with respect to baseline. Furthermore, patients in the inhaled drug groups were weaned easily from cardiopulmonary bypass ($P = 0.04$) and had a shorter intubation time ($P = 0.03$) and intensive care unit stay ($P = 0.02$) than the control group.**

Conclusions **Our data suggest that both iNO and $iPGI_2$ are effective in the treatment of pulmonary hypertension. $iPGI_2$ has a number of advantages over iNO, including its easy administration and lower cost. Intravenous vasodilator treatment, on the other hand, is effective in terms of mortality but has a higher morbidity rate.** ***J Cardiovasc Med*** **7:119–123 © 2006 Italian Federation of Cardiology.**

Journal of Cardiovascular Medicine 2006, **7**:119–123

Keywords: cardiac surgical procedures, nitric oxide, prostacyclin, pulmonary hypertension, right ventricular function, vasodilators

[a]Unit of Cardiac Surgery, University of Palermo, Palermo, Italy and [b]Department of Cardiac and Respiratory Diseases, ''La Sapienza'' University, Rome, Italy

Correspondence to Dr Khalil Fattouch, Via Mariano Stabile 172, 90139 Palermo, Italy
e-mail: khalilfattouch@hotmail.com

Received 4 March 2005 **Revised** 30 June 2005
Accepted 4 July 2005

Introduction

Pulmonary hypertension in patients undergoing cardiac surgery is associated with increased mortality and morbidity rates [1]. Mitral valve stenosis is frequently associated with an increase in pulmonary vascular resistance (PVR); cardiopulmonary bypass (CPB) may exacerbate pulmonary hypertension, resulting in acute right ventricular dysfunction. The cause of pulmonary hypertension is multifactorial but is probably a combination of a preexisting pulmonary hypertension exacerbated by CPB-induced damage to the pulmonary endothelium with a further loss of the vasodilator function [2–9]. The administration of vasoactive agents by inhalation, so that vasodilation is confined to the pulmonary circulation, has improved the management of pulmonary hypertension in cardiac surgery patients. The two inhaled agents that have been investigated in this respect are inhaled nitric oxide (iNO) and prostacyclin ($iPGI_2$). $iPGI_2$ appears to be a selective pulmonary vasodilator acting through cAMP instead of cGMP [10,11]. Its half life is 2–3 min, and at physiological pH, it spontaneously hydrolyses to 6-keto-prostaglandin-$F1_\alpha$. Thus, its effect remains localized to ventilated lung units and it can decrease pulmonary artery pressure, without causing systemic hypotension, and improve oxygenation by decreasing ventilation–perfusion mismatch [12–14]. Its effect on cardiac function is controversial but it can increase cardiac output when given intravenously [15,16]. The

1558-2027 © 2006 Italian Federation of Cardiology

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

inhalation of NO was demonstrated to selectively reduce pulmonary hypertension and improve the ventilation–perfusion ratio [10,17]. iNO reacts with oxygen to form nitrite anion. NO is converted to nitric and nitrous acids. Peroxynitrite is formed when NO reacts with superoxide anion radical and is highly cytotoxic. Combination of NO and haemoglobin rapidly produces nitrosyl Fe(II)-haemoglobin and then methaemoglobin. Clinically significant methaemoglobinaemia is rare after low level NO exposure. NO toxic effects, related to methaemoglobinaemia and nitrogen dioxide, are dose-related. A paradoxical decrease in systemic oxygenation has been observed at higher doses of iNO. It is hypothesized that higher doses of NO may result in a diffusion of NO to lung regions that are not well ventilated and consequently promote a ventilation–perfusion inequality.

The present study was carried out to compare iNO and $iPGI_2$ with intravenous vasodilators and vasoactive agents, which are the drugs commonly used in treatment of pulmonary hypertension during cardiac surgery in adults.

Methods

This prospective, randomized study included 58 patients affected by severe mitral valve stenosis with high PVR (> 250 dynes·s·cm^{-5}) who underwent mitral valve repair or replacement. All patients signed an informed consent. Patients were randomized into three groups: $iPGI_2$ group, iNO group, and control group (treated with traditional intravenous vasodilators). Patients were considered to have pulmonary hypertension if systolic pulmonary artery pressure was > 45 mmHg or the mean pulmonary artery pressure (MPAP) was > 25 mmHg, as measured during the preoperative period or estimated by using Doppler echocardiography [18]. Data were confirmed after insertion of a pulmonary catheter (Swan–Ganz). The following exclusion criteria were used: left ventricular dysfunction (ejection fraction $< 30\%$), emergency operative status, diathesis, known coagulopathy, thrombocytopenia, and concomitant cardiac procedures.

In all patients, anaesthesia was induced with sufentanil (1 μg/kg), pancuronium bromide (0.1 mg/kg) and midazolam (0.05 mg/kg) and maintained with continuous infusions of sufentanil (1 μg/kg/h) and midazolam (0.04 mg/kg/h). No anaesthetic gas was used. Minute ventilation was adjusted to maintain end-tidal carbon dioxide between 30 and 40 mmHg. A 5.0 MHz transoesophageal omniplane probe (Hewlett-Packard Sonos 4500, Hewlett-Packard, Andover, Massachusetts, USA) was inserted after induction of general anaesthesia. A transoesophageal echocardiographic examination was performed to evaluate systolic and diastolic parameters of left and right ventricular performance.

Normothermic cardiopulmonary bypass was conducted in all patients. A continuous flow of 2–2.5 l/min/m^2 and a perfusion pressure between 50 and 70 mmHg was kept. Intermittent antegrade cold blood cardioplegia was used for myocardial protection.

The following haemodynamic parameters were measured or calculated: heart rate, systolic, diastolic and mean arterial pressure, cardiac index, stroke volume, systolic and diastolic pulmonary artery pressure, MPAP, central venous pressure, pulmonary capillary wedge pressure, systemic vascular resistance, PVR, and right ventricular ejection fraction. Data were recorded at the following times: T1, at baseline (before induction of anaesthesia); T2, after heparin dose; T3, at CPB interruption (drug administration); T4, after protamine; T5, at chest closure; T6, 2 h before arrival at the intensive care unit. The average dose of inotropic and pressor agents administered intraoperatively was recorded for each patient.

Drug administration protocol

Epoprostenol (Flolan, Glaxo-Wellcome Inc., Mississauga, Canada) was given as epoprostenol salt 1.5 mg dissolved in a sterile glycine buffer diluent for a concentration of 15 μg/ml. The drug was administered through a jet nebulizer connected to the inspiratory limb of the ventilator near the endotracheal tube. Nebulization was achieved with an oxygen flow of 8 l/min. This high flow was used to achieve a high proportion of small particles (< 5 μm). Because this added a secondary flow to the patient, minute ventilation was adjusted to maintain peak inspiratory pressures of < 30 cm H_2O and a normal end-tidal carbon dioxide.

NO was supplied as a 400 ppm mixture diluted in nitrogen. The NO/nitrogen mixture was delivered by an NO delivery device (INOvent, Ohmeda Inc., Madison, Wisconsin, USA). This delivery device is capable of providing a user-selected consistent concentration of inspired iNO, regardless of ventilator volume and flow setting. The final blended gas was then introduced into the inspiratory limb of the respiratory circuit. The inhaled concentration of NO was determined by the INOvent delivery device using electrochemical cell analysis with sampling of the inspired gases at the distal inspiratory limb of the breathing circuit occurring in a continuous fashion. Although significant methaemoglobinaemia is rare after low level NO exposure, its serum levels were measured after 30 min of exposure to iNO; patients with serum levels $> 4\%$ were monitored every 2 h. Drugs were given immediately before the interruption of CPB and discontinued at least 60 min after exposure.

Statistical analysis

Data were expressed as mean ± SD. Data were statistically analysed using standard analyses of variance

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

Table 1 Preoperative and perioperative patient characteristics

	$iPGI_2$ group ($n = 19$)	iNO group ($n = 21$)	Control group ($n = 18$)
Age (years)	62 ± 8	65 ± 9	64 ± 7
Atrial fibrillation	8	7	10
NYHA functional class	3.5 ± 0.5	3.3 ± 0.6	3.6 ± 0.4
Anticoagulant therapy	11	14	8
Redo	2	1	0
Procedures			
MVS	14	15	13
MVS + TVR	5	6	5
CPB (min)	$77 \pm 12^*$	$72 \pm 14^*$	99 ± 15
Aortic cross-clamping (min)	48 ± 8	46 ± 10	42 ± 11
Bleeding (ml)	640 ± 220	580 ± 230	520 ± 210
Intubation (h)	$18 \pm 4.2^*$	$20 \pm 3.1^*$	31 ± 3.2
ICU stay (h)	$45 \pm 12^*$	$48 \pm 11^*$	78 ± 38
In-hospital stay (days)	10 ± 3	9 ± 2.8	14 ± 6
In-hospital mortality	0	1	1
Reoperation for bleeding	1	0	2

CPB = cardiopulmonary bypass; ICU = intensive care unit; iNO = inhaled nitric oxide; $iPGI_2$ = inhaled prostacyclin; MVS = mitral valve surgery; NYHA = New York Heart Association; TVR = tricuspid valve repair. $^*P < 0.05$ for the $iPGI_2$ and iNO groups compared with the control group.

(ANOVA) in conjunction with Student-Newman–Keuls multiple comparison tests. All tests were two-sided. A two-way ANOVA (group by time) with time as a repeated measure factor was performed on the variables heart rate, mean arterial pressure, MPAP, cardiac index, PVR and systemic vascular resistance, using the values from post-bypass to arrival at the intensive care unit. When either the groups' effects were significant ($P < 0.05$) or a significant interaction (group by time) was present, an analysis at each time point was performed. A P value of < 0.05 was considered statistically significant.

Results

The three groups did not differ statistically with regard to demographic data or New York Heart Association functional classification (Table 1). The three groups also did not differ statistically with respect to surgical and anaesthesia treatment. Hospital mortality was 3.4% (one patient died for right ventricular failure in the iNO group and one for uncontrolled bleeding in the control group). Baseline, intraoperative and postoperative haemodynamic parameters are shown in Table 2. There were no statistically significant differences in the baseline data among the three groups.

After induction of anaesthesia (T2), MPAP and PVR were decreased with respect to baseline (T1), but the difference did not reach statistical significance. After drug administration (T3), MPAP and PVR were significantly decreased with respect to baseline ($P < 0.05$) and maintained throughout the study; this was not observed in the control group. The right ventricular ejection fraction was also significantly increased at T5 and T6 with respect to T1 and a statistically significant difference was observed in the iNO and $iPGI_2$ groups with respect to the control group and to baseline. Moreover, in the patients who received iNO and $iPGI_2$, we observed a statistically significant increase in the cardiac indices at T3, T5 and T6 as compared with baseline and the control group. Patients in the inhaled drug groups were weaned easily from CPB with respect to the control group ($P = 0.04$) and a significant difference was observed for time of intubation ($P = 0.03$) and intensive care unit stay ($P = 0.02$) (Table 1). Patients in the control group needed higher doses of inotropic and vasopressor drugs than patients in the iNO and $iPGI_2$ groups (Table 3). No adverse effects were observed due to drug administration.

Discussion

The cause of pulmonary hypertension in cardiac surgery patients is multifactorial but is probably a combination of a preexisting pulmonary hypertension, due to the cardiac pathology, exacerbated by CPB. We know that CPB induces pulmonary endothelial cell injury and pulmonary dysfunction, probably due to hypoperfusion of the lung during CPB or activation of the systemic inflammatory response, which exacerbates the reactivity of the pulmonary vascular bed. This may result in inhibition of NO production and an increase in the production of endothelin-1 after CPB [19,20]. Pulmonary hypertension may be of sufficient severity to produce acute right ventricular failure and an inadequate cardiac output. Treatment of this condition has always been challenging. Most intravenous agents that dilate the pulmonary vasculature, such as dobutamine, nitroglycerin, milrinone, sodium nitroprusside, and calcium channel antagonists, can cause systemic hypotension. Systemic hypotension will decrease coronary artery perfusion to the right ventricle at a time when right ventricular end-diastolic pressures are high and right ventricular coronary perfusion pressure is already likely to be low. Administering the vasodilator agents by inhalation, so that vasodilation is confined to the pulmonary circulation, has improved the management of this condition. The role of NO and PGI_2 as specific pulmonary vasodilators in the setting of adult cardiac surgery is well established. Previous studies,

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

Table 2 Haemodynamic data

	T1	T2	T3	T4	T5	T6
HR (b/min)						
iNO group	80 ± 23	76 ± 17	106 ± 15	103 ± 17	109 ± 16	98 ± 18
$iPGI_2$ group	76 ± 19	81 ± 9	91 ± 13	99 ± 18	91 ± 18	101 ± 16
Control group	82 ± 20	80 ± 13	93 ± 11	96 ± 12	103 ± 11	93 ± 12
MAP (mmHg)						
iNO group	79 ± 10	78 ± 9	83 ± 11	81 ± 8	86 ± 9	85 ± 11
$iPGI_2$ group	82 ± 11	78 ± 11	69 ± 8	79 ± 12	90 ± 8	95 ± 12
Control group	80 ± 9	80 ± 8	70 ± 12	68 ± 10	70 ± 12	68 ± 12
MPAP (mmHg)						
iNO group	38 ± 6	32 ± 5	22 ± 5*,§	23 ± 5*,§	20 ± 3*,§	22 ± 6*,§
$iPGI_2$ group	42 ± 11	35 ± 7	24 ± 4*,§	22 ± 6*,§	26 ± 9*,§	24 ± 5*,§
Control group	38 ± 8	33 ± 8	35 ± 4	35 ± 6	33 ± 5	35 ± 5
PCWP (mmHg)						
iNO group	23 ± 6	21 ± 5	16 ± 6*	16 ± 5*	15 ± 3*	16 ± 4*
$iPGI_2$ group	25 ± 8	22 ± 7	17 ± 8*	16 ± 6*	17 ± 5*	16 ± 5*
Control group	24 ± 6	22 ± 8	21 ± 6	19 ± 8	22 ± 7	21 ± 6
CI (l/min)						
iNO group	2.9 ± 0.4	3.2 ± 0.5	3.9 ± 0.4*,§	3.5 ± 0.6	4.1 ± 0.6*,§	3.9 ± 0.6*,§
$iPGI_2$ group	2.8 ± 0.6	2.9 ± 0.2	3.7 ± 0.6*,§	3.4 ± 0.3	3.7 ± 0.6*,§	3.8 ± 0.5*,§
Control group	2.8 ± 0.5	2.9 ± 0.4	2.7 ± 0.5	2.6 ± 0.2	2.7 ± 0.4	2.6 ± 0.2
PVR (dynes·s·cm^{-5})						
iNO group	495 ± 210	416 ± 185	236 ± 102*,§	211 ± 95*,§	235 ± 115*,§	235 ± 98*,§
$iPGI_2$ group	515 ± 220	445 ± 210	215 ± 95*,§	195 ± 102*,§	225 ± 122*,§	205 ± 105*,§
Control group	475 ± 216	459 ± 198	367 ± 205	312 ± 178	355 ± 185	385 ± 150
SVR (dynes·s·cm^{-5})						
iNO group	1720 ± 351	1494 ± 541	1420 ± 451	1390 ± 289	1406 ± 382§	1480 ± 381§
$iPGI_2$ group	1890 ± 407	1590 ± 709	1320 ± 467	1420 ± 237	1320 ± 331§	1310 ± 353§
Control group	2074 ± 592	1864 ± 862	1974 ± 382	2074 ± 266	2214 ± 466	2274 ± 466
RVEF (%)						
iNO group	29 ± 12	30 ± 10	36 ± 8	35 ± 12	39 ± 10*,§	42 ± 9*,§
$iPGI_2$ group	28 ± 14	29 ± 11	35 ± 11	34 ± 11	38 ± 11*,§	43 ± 11*,§
Control group	30 ± 12	33 ± 9	30 ± 9	30 ± 12	31 ± 8	32 ± 7

Data are expressed as mean ± SD. CI = cardiac index; HR = heart rate; iNO = inhaled nitric oxide; $iPGI_2$ = inhaled prostacyclin; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RVEF = right ventricular ejection fraction; SVR = systemic vascular resistance; T1 = baseline (before induction of anaesthesia); T2 = after heparin dose; T3 = cardiopulmonary bypass interruption (after drug administration); T4 = after protamine; T5 = at chest closure; T6 = 1 h before arrival at the intensive care unit. *$P < 0.05$ at each signed time compared with T1; §$P < 0.05$ for the $iPGI_2$ and iNO groups compared with the control group.

however, have prospectively compared the treatment of pulmonary hypertension with the different drugs available [10,11,13]. The present study sought to determine the different effects that iNO and $iPGI_2$ therapies have on haemodynamic parameters and on the consequent requirement of inotropic and pressor agents. Moreover, we aimed at comparing the effects of iNO and $iPGI_2$ with respect to intravenous vasodilator therapy (nitroglycerin or nitroprusside). Our data demonstrated that MPAP and PVR, after weaning from CPB, were equally decreased in both the inhaled drug groups (iNO and $iPGI_2$). In the control group, MPAP and PVR were decreased but there was no statistically significant difference as compared to baseline. Transoesophageal echocardiography showed a progressive improvement in right ventricular ejection fraction with respect to preoperative contractile function in the iNO and $iPGI_2$ groups; this improvement reached a statistical significance in the intensive care unit as compared with the preoperative condition.

This study suggests that patients with pulmonary hypertension who are treated with iNO or $iPGI_2$ require less vasopressor agent and CPB support postoperatively than patients treated with intravenous vasodilators. Probably, treatment of pulmonary hypertension with intravenous vasodilators, such as nitroglycerin or nitroprusside, can produce pulmonary and systemic hypotension that require higher doses of vasopressor agents to support the systemic pressure by inotropic effect and systemic vasoconstriction. The requirement of inotropic support is an indication of haemodynamic instability. Additionally, morbidity is associated with the use of pressor agents in terms of altered organ perfusion, arrhythmias, and pulmonary vasoconstriction. The greater requirement and use of the vasoactive agents in the group of patients who were treated with intravenous vasodilators would be expected to produce a deleterious effect on PVR and consequently right ventricular ejection fraction. Despite having the lowest initial PVR, the control group had the highest PVR in the intensive care unit. Although PGI_2 is a powerful inhibitor of platelet aggregation, this effect has not been shown to occur when it is administered by means of inhalation. Our data confirm other findings [12,21,22]. Moreover, the typical symptoms of headache, facial flushing, arthralgias, nausea, and jaw pain associated with intravenous administration are not observed with inhaled therapy [23], suggesting that systemic absorption is minimal.

In conclusion, these data suggest that both iNO and $iPGI_2$ are effective in the treatment of pulmonary hypertension. $iPGI_2$ has a number of advantages over iNO,

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

Table 3 Mean dose of inotropes and vasopressor agents used after bypass surgery and in the intensive care unit

	$iPGI_2$ goup	iNO group	Control group
Dobutamine	3.1 ± 0.9	2.9 ± 0.6	4.1 ± 1.1
Dopamine	$2.9 \pm 0.9^*$	$3.1 \pm 0.5^*$	5.3 ± 2.1
Adrenaline	$0.0 \pm 0.0^*$	$0.01 \pm 0.009^*$	0.06 ± 0.02
Noradrenaline	$0.0 \pm 0.0^*$	$0.0 \pm 0.0^*$	0.03 ± 0.02

Data are expressed as mean $\pm$ SD. iNO = inhaled nitric oxide; $iPGI_2$ = inhaled prostacyclin. $^*P < 0.05$ for the $iPGI_2$ and iNO groups compared with the control group.

including its easy administration (which is both simple and inexpensive in the case of PGI_2), treatment cost (significantly less for PGI_2), and the fact that in contrast to iNO, neither PGI_2 nor its metabolites have any known toxic effects. On the other hand, the traditional treatment is effective in terms of mortality but not of morbidity.

Study limitations

The main limitation of this study is the small number of patients enrolled in each group. This might not have been sufficient to observe a statistically significant difference on outcomes or evidence could be not realistic.

Moreover, only one dose was studied. We did not explore the dose–response curve of iNO and $iPGI_2$. The dose used was based on previous experience with the drug. The quantity of drug that reaches the lungs, when administering drugs by means of nebulization, is highly variable. It depends on the characteristics of the drug itself, the nebulizer used, the characteristics of the carrier gas, the amount of the drug remaining in the nebulizer, and the humidity and temperature in the nebulizer circuit. Particles of 1–5 μm are considered to be in the respirable range.

Acknowledgements

We thank Prof. Raffaele Masciangelo from the Institute of Experimental Medicine and Pathology of ''La Sapienza'' University of Rome for statistical analysis, and Dr Stefania Lanzara for revisions and final editing of the manuscript.

References

1 Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. *Ann Thorac Surg* 2000; **69**: 823–828.
2 Lesage AM, Tsuchioka H, Young WG Jr, Sealy WC. Pathogenesis of pulmonary damage during extracorporeal perfusion. *Arch Surg* 1966; **93**:1002–1008.
3 Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. *J Am Coll Cardiol* 1992; **19**:48–54.
4 Speziale G, De Biase L, De Vincentis G, Lerardi M, Ruvolo G, La Francesca S, *et al.* Inhaled nitric oxide in patients with severe heart failure: changes in lung perfusion and ventilation detected using scintigraphy. *Thorac Cardiovasc Surg* 1996; **44**:35–39.
5 Kirklin JK, Naftel DC, McGiffin DC, McVay RF, Blackstone EH, Karp RB. Analysis of morbid events and risk factors for death after cardiac transplantation. *J Am Coll Cardiol* 1988; **11**:917–921.
6 Downing SW, Edmunds LH Jr. Release of vasoactive substances during cardiopulmonary bypass. *Ann Thorac Surg* 1992; **54**:1236–1243.
7 Ruvolo G, Speziale G, Greco E, Tritapepe L, Mollace V, Nistico G, Marino B. Nitric oxide release during hypothermic versus normothermic cardiopulmonary bypass. *Eur J Cardiothorac Surg* 1995; **9**:651–654.
8 Speziale G, Ruvolo G, Marino B. A role for nitric oxide in the vasoplegic syndrome. *J Cardiovasc Surg (Torino)* 1996; **37**:301–303.
9 Ruvolo G, Greco E, Speziale G, Tritapepe L, Marino B, Mollace V, Nistico G. Nitric oxide formation during cardiopulmonary bypass. *Ann Thorac Surg* 1994; **57**:1055–1057.
10 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**:780–786.
11 Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller m, *et al.* Inhaled prostacyclin (PGI_2) versus inhaled nitric oxide in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **154 (Pt 1)**:1671–1677.
12 Van Heerden PV, Barden A, Michalopoulos N, Bulsara MK, Roberts BL. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest* 2000; **117**:819–827.
13 Olschewski H, Walmrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996; **124**:820–824.
14 Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolized prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; **342**:961–962.
15 Montalescot G, Drobinski G, Meurin P, Maclouf J, Sotirov I, Philippe F, *et al.* Effects of prostacyclin on the pulmonary vascular tone and cardiac contractility of patients with pulmonary hypertension secondary to end-stage heart failure. *Am J Cardiol* 1998; **82**:749–755.
16 Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 1999; **34**:1184–1187.
17 Girard C, Lehot JJ, Pannetier JC, Filley S, Ffrench P, Estanove S. Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. *Anesthesiology* 1992; **77**:880–883.
18 Moraes D, Loscalzo J. Pulmonary hypertension: newer concepts in diagnosis and management. *Clin Cardiol* 1997; **20**:676–682.
19 Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation* 1993; **88 (Pt 1)**:2128–2138.
20 Komai H, Adatia IT, Elliott MJ, de Leval MR, Haworth SG. Increased plasma levels of endothelin-1 after cardiopulmonary bypass in patients with pulmonary hypertension and congenital heart disease. *J Thorac Cardiovasc Surg* 1993; **106**:473–478.
21 Haraldsson A, Kieler-Jensen N, Ricksten SE. Inhaled prostacyclin for treatment of pulmonary hypertension after cardiac surgery or heart transplantation: a pharmacodynamic study. *J Cardiothorac Vasc Anesth* 1996; **10**:864–868.
22 Haraldsson A, Kieler-Jensen N, Wadenvik H, Ricksten SE. Inhaled prostacyclin and platelet function after cardiac surgery and cardiopulmonary bypass. *Intensive Care Med* 2000; **26**:188–194.
23 Olschewski H, Ghofrani A, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, Seeger W. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Respir Crit Care Med* 1999; **160**:600–607.

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.