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Comparison of the Usage of Intravenous Iloprost and Nitroglycerin for Pulmonary Hypertension during Valvular Heart Surgery

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ABSTRACT

Background. Pulmonary hypertension secondary to valvular heart disease is a cause of acute right heart failure during valve replacement operations. This study compares the hemodynamic effects of intravenous use of iloprost and nitroglycerin in patients with pulmonary hypertension undergoing valvular replacement surgery. We sought to determine the acceptable doses of these medications for use in surgery to decrease mean pulmonary artery pressure to <30 mmHg without causing systemic side effects. The plasma nitric oxide levels that were obtained from pulmonary mixed venous blood have been compared to demonstrate the difference in the action mechanism of these drugs.

Methods. Eighteen patients undergoing mitral or aortic and mitral valvular replacement with pulmonary hypertension >25 mmHg were included in the study. The 2 groups received iloprost or nitroglycerin via a central pulmonary catheter, and the hemodynamic parameters were evaluated before incision (T1), 10 minutes after chest opening (T2), and 5 minutes and 20 minutes after cardiopulmonary bypass (T3 and T4). The plasma nitric oxide levels were obtained from the mixed venous blood at the T1 and T4 intervals.

Results. The data have been analyzed for each group and for repeated measurements of hemodynamic parameters at T1-T4 time points. The analysis of hemodynamic parameters before (T1 and T2) and after (T3 and T4) bypass showed similar responses depending on the use of either iloprost or nitroglycerin. The administration of iloprost after bypass (T3) at a dosage of 1.25 to 2.5 ng/kg per minute reduced mean pulmonary artery pressure (from 28.8 ± 7.89 to 20.63 ± 6.39 mmHg) and pulmonary vascular resistance (from 226.88 ± 101.93 to 118.00 ± 82.36 dyn sec cm –5) better than nitroglycerin at a dosage of 0.5 to 1 μg/kg per minute (from 23.20 ± 5.20 to 18.50 ± 5.10 mmHg and from 160.80 ± 39.76 to 137.40 ± 56.54 dyn sec cm –5, respectively). Iloprost causes significant increase in cardiac output (from 4.91 ± 0.91 to 5.49 ± 0.91 L/min) compared to nitroglycerin (from 5.23 ± 0.80 to 5.27 ± 0.74 L/min). The plasma nitric oxide levels of the iloprost group did not show an increase from T1 to T4, whereas the nitroglycerin group levels did (P <.05).

Conclusions. Intravenous use of both iloprost and nitroglycerin effectively reduces mean pulmonary artery pressure, although only the iloprost group was accompanied by an increase in cardiac output. During operation, where abrupt management of pulmonary hypertension is required, systemic use of iloprost or nitroglycerin at appropriate doses via a pulmonary artery catheter offers adequate relief of hypertension and is well tolerated without any significant adverse effects. The plasma nitric oxide levels did not rise with the use of iloprost.

INTRODUCTION

Pulmonary hypertension secondary to valvular heart disease is an important risk factor in the development of increased pulmonary artery pressures and acute right heart failure (RHF) after cardiopulmonary bypass (CPB) [Kaul 2000]. Pulmonary hypertension is an elevation of pulmonary vascular resistance (PVR) due to the progressive reduction in the distensibility of the pulmonary vascular bed. This process presents clinically with the elevation of the mean pulmonary artery pressures (MPAP) and provides a valuable parameter regarding impending RHF [Galie 2001]. Impaired right ventricular (RV) function is associated with a poor outcome in the surgical setting. The mortality rate of patients with combined arterial hypotension and severe RV dysfunction after CPB can reach 86% [Reichert 1992].

Iloprost is a stable carbacyclin derivative of prostaglandin I_2 (PGI_2). PGI_2 was named prostacyclin in 1976 by Moncada [Moncada 1976]. The endothelial cells most actively produce PGI_2 and cause relaxation of vascular smooth muscle through the activation of adenylate cyclase and increased production of cyclic adenosine monophosphate. Nitroglycerin induces smooth muscle relaxation by the endogenous release of nitric oxide. This substance acts through the activation of soluble guanylate cyclase that leads to an increase of the second messenger cyclic guanosine monophosphate in the vascular smooth muscle cells [Grant 1992]. Cyclic guanosine

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Table 1. Demographic Data of the Study Patients*

Patient, N	Age, y	Sex, M:F	Height, cm	Weight, kg	Diagnosis	Baseline MPAP, mmHg
1	53	M	1.65	52	AS+MS	42
2	58	F	1.48	58	MS+MR	39
3	52	F	1.50	69	MS+MR	46
4	53	M	1.56	56	MS	35
5	57	F	1.60	55	MS	35
6	48	F	1.55	55	AS+AR+MS	55
7	63	M	1.62	61	MS+MR	40
8	38	F	1.65	64	AS+MS+MR	42
9	53	F	1.60	74	MS+MR	35
10	50	F	1.55	57	MS+MR	35
11	70	F	1.54	58	MS	35
12	65	F	1.65	55	MS	30
13	25	M	1.78	70	AS+AR+MS	55
14	44	M	1.73	75	AS+MS	50
15	71	M	1.65	56	MS	40
16	44	F	1.60	74	MS+MR	45
17	32	M	1.65	68	MS	35
18	43	M	1.85	60	AS+AR+MS+MR	55
Mean ± SD	51.06 ± 12.31		1.62 ± 0.09	62.05 ± 7.63		41.75 ± 8.06

*MPAP indicates mean pulmonary artery pressure; AS, aortic stenosis; MS, mitral stenosis; MR, mitral regurgitation; AR, aortic regurgitation.

monophosphate is rapidly metabolized by phosphodiesterases, thereby terminating the effect of nitric oxide (NO). Iloprost has advantages over PGI_2, including its solubility in saline, which obviates the need for an alkaline buffer and a lower viscosity, which causes significantly longer action duration. The plasma half life of iloprost is 20 to 30 minutes.

This study evaluates the hemodynamic response to the use of intravenous iloprost and nitroglycerin during valvular heart surgery. We sought to determine the acceptable doses of these medications for use in surgery to decrease MPAP to <30 mmHg without causing systemic side effects. The plasma nitric oxide levels that were obtained from pulmonary mixed venous blood have been compared to demonstrate the difference in the action mechanism of these drugs.

MATERIALS AND METHODS

Patients

In this study, we randomly enrolled 18 patients who were scheduled for mitral or aortic and mitral valve surgery and had presented pulmonary hypertension (MPAP >25 mmHg) in their echocardiography report. Their ages ranged from 25 to 71 years old. The replacement of aortic and mitral valves was done in 6 of these patients and only mitral valve replacement was done in 12 patients. Left ventricle ejection fractions were between 35% and 55% for all patients. Patients were in New York Heart Association (NYHA) functional class III or IV despite medical therapy. After approval from the Ethics Committee of the hospital, each patient gave informed consent before surgery. In the nitroglycerin group (group 1, n = 10), the mean ± standard deviation of the ages was 52.50 ± 2.10, and in the iloprost group (group 2, n = 8) it was 49.25 ± 6.17. The demographic data of each group is shown in Table 1.

There were 8 men (44%) and 10 women (66%). In Table 1, the first 10 patients were in group 1 and the next 8 patients presents were in group 2. The mean ± standard deviation of baseline MPAP for group 1 was 40.40 ± 6.40 and for group 2 it was 43.13 ± 9.61. The baseline MPAP values were preoperatively obtained from the echocardiography study report.

Hemodynamic Measurements

The pulmonary artery catheter was placed after induction of anesthesia via the right internal jugular vein using an 8.5 Fr introducer sheath and 8 French Swan Ganz catheter (Swan Ganz IntelliCath; Baxter Healthcare, Irvine, CA, USA). Cardiac output (CO) determinations were made in triplicate using the thermodilution technique and a computer system (Baxter Healthcare). Arterial blood pressure and arterial blood gases were monitored via an arterial line (20 Gauge catheter; B. Braun, Bethlehem, PA, USA). Mixed venous blood samples were obtained from the pulmonary artery catheter tip along with arterial samples for each intervention (T1-T4).

Conduct of Anesthesia, Myocardial Preservation, and Surgery

After the induction of anesthesia with intravenous fentanyl (10 μg/kg), propofol (1 mg/kg), and pancuronium (0.1 mg/kg) anesthetic maintenance was provided with fentanyl infusion (0.5 μg/kg per minute), isoflurane (0.4-1.0%), and propofol (1 mg/kg). The lungs were ventilated with 100% O_2 during surgery. CPB was established with arterial cannulation and drainage with return via a venous cannula. Cold blood cardioplegia was delivered. The patients were cooled to 32°C. A membrane oxygenator (Quadrox; Jostra, Hirrlingen, Germany) and a roller pump (Jostra) were used to provide nonpulsatile bypass (bypass flow: 2.4 L/m^2

Table 2. Hemodynamic Variables at Each Measurement and *P* Values for Each Group and for Repeated Measurements*

Parameters	*P*	*P*-Repeated		T1	T2	T3	T4
HR	.509	.001	Group 1	90.40 ± 13.14	99.20 ± 8.89	102.40 ± 9.56	106 ± 9.09
			Group 2	91.38 ± 13.71	95.38 ± 8.60	100.4 ± 10.81	101.4 ± 11.94
MAP	.658	.000	Group 1	86.80 ± 18.40	70.00 ± 11.65	70.50 ± 9.35	68.80 ± 6.14
			Group 2	82.63 ± 10.84	71.75 ± 7.07	71.88 ± 6.38	76.00 ± 4.31
CVP	.262	.304	Group 1	9.30 ± 4.42	7.90 ± 2.18	8.10 ± 1.97	8.40 ± 1.58
			Group 2	9.88 ± 3.52	9.25 ± 2.87	9.50 ± 3.02	10.38 ± 2.45
PAWP	.047	.000	Group 1	15.20 ± 2.86	13.20 ± 1.93	14.80 ± 4.02	11.40 ± 2.95
			Group 2	18.50 ± 3.63	14.13 ± 2.85	16.50 ± 2.33	13.50 ± 2.07
MPAP	.106	.000	Group 1	27.90 ± 4.75	21.10 ± 3.90	23.20 ± 5.20	18.50 ± 5.10
			Group 2	33.00 ± 6.76	22.38 ± 5.45	28.38 ± 7.89	20.63 ± 6.39
CO	.609	.000	Group 1	4.91 ± 0.62	5.01 ± 0.55	5.23 ± 0.80	5.27 ± 0.74
			Group 2	4.24 ± 1.02	5.03 ± 0.98	4.91 ± 0.91	5.49 ± 0.91
SVR	.370	.000	Group 1	1261 ± 287	993 ± 205	977 ± 229	932 ± 156
			Group 2	1464 ± 509	1023 ± 227	1070 ± 292	987 ± 230
PVR	.256	.000	Group 1	196 ± 61	130 ± 43	161 ± 40	137 ± 57
			Group 2	283 ± 99	117 ± 53	227 ± 102	118 ± 82
SaO_2	.074	.308	Group 1	98.2 ± 0.79	98.2 ± 0.92	97.7 ± 0.95	98.2 ± 0.92
			Group 2	98.6 ± 0.52	98.5 ± 0.54	98.38 ± 0.74	98.63 ± 0.52
SvO_2.	.03	.003	Group 1	75.90 ± 4.23	75.30 ± 4.00	75.70 ± 5.35	76.10 ± 5.61
			Group 2	76.53 ± 5.59	81.00 ± 4.84	76.40 ± 4.07	85.00 ± 4.66
Dobutamin, μg/kg per minute			Group 1			5	5
			Group 2			5	5
Nitroglycerin, μg/kg per minute			Group 1	0.5-1	0.5-1	0.5-1	0.5-1
			Group 2	0.5-1	0.5-1	0.5-1	0.5-1
Iloprost, ng/kg per minute			Group 1	1.25-2.5	1.25-2.5	1.25-2.5	1.25-2.5

*T1 and T2 are pre-cardiopulmonary bypass measurements. T3 and T4 are post-cardiopulmonary bypass measurements. For repeated measurements (T1-T4) *P* <.05 is statistically significant. HR indicates heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PAWP, pulmonary artery wedge pressure; MPAP, mean pulmonary artery pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation.

per minute). Once valve replacement was completed and the cross clamp was opened the patient was weaned from bypass. Blood products were used, bleeding was controlled, the sternum was closed, and the patient was returned to the intensive care unit.

Study Protocol

Hemodynamic measurements were obtained after the induction of anesthesia (T1) and 15 minutes after the administration of either nitroglycerin or iloprost via the pulmonary artery catheter (T2). No medications were administered during bypass. The measurements were repeated after the bypass period before administration of either drug (T3), and after the administration of either drug another measurement was obtained within 15 minutes (T4). Nitroglycerin 10 mg/mL (Perlinganit; Santa Farma, Istanbul, Turkey) diluted in 100 mL 0.9% isotonic sodium chloride was administered at a dosage of 0.5 to 1 μg/kg per minute via a pulmonary artery catheter. Iloprost 20 μg/ml (Ilomedin; Shering AG, Berlin, Germany), which has been approved by the Ministry of Health for general use in patients, was diluted in 100 mL 0.9% isotonic sodium chloride solution. Intravenous iloprost was administered at a dosage of 1.25 to 2.5 ng/kg per minute. Inotropic support of dobutamin 5 μg/kg per minute was administered after the bypass period. The study protocol did not continue in the postoperative period.

For plasma nitric oxide levels, blood samples were obtained from the pulmonary artery catheter tip before and after administration of either drug at the T1 and T4 timings (Sievers 280i Nitric Oxide Analyzer; General Electric, Boulder, CO, USA). The determination of NO metabolites, NO-2, and NO-3 measurements were done and the data have been presented in μM/mL.

Statistical Analysis

All variables are presented as mean ± standard deviation. Statistical procedures were performed using SPSS 13.0 (SPSS, Chicago, IL, USA). First variables were tested for normal distribution with a Kolmogorov-Smirnov test. All variables passed this test. Two groups for 4 repeated measures were tested with analysis of variance, and when the f score was significant (*P* <.05) a post hoc analysis was performed with least square difference to examine the differences between means. For the nitric oxide measurements, 2 groups were compared with the Wilcoxon signed rank test using median values and the percent of change between the 2 groups ([T1-T4]/T1 * 100) was calculated with the Mann-Whitney U test. A value of *P* <.05 was considered statistically significant.

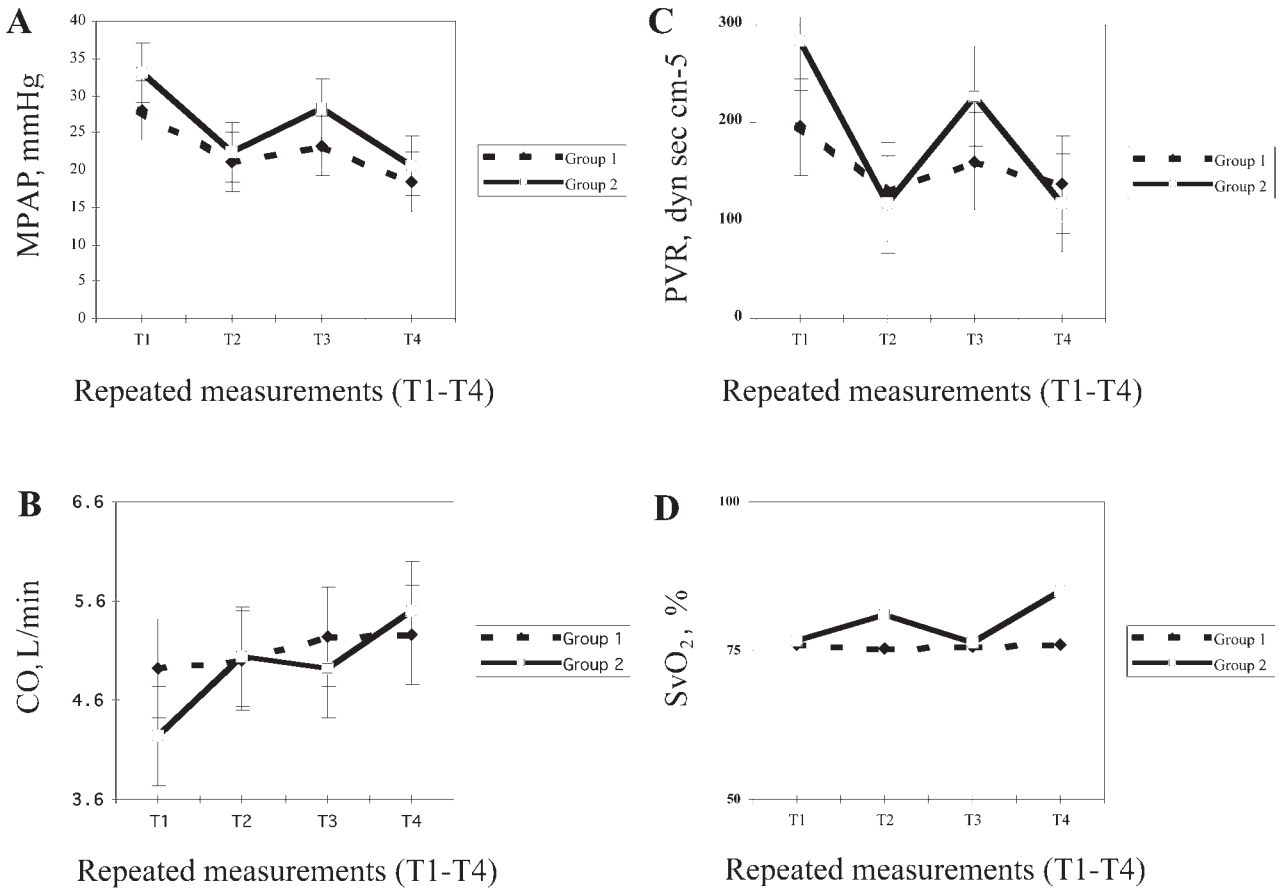

Figure. Comparison of the effects of intravenous nitroglycerin (group 1) at a dosage of 0.5 to 1 µg/kg per minute and intravenous iloprost (group 2) at a dosage of 1.25 to 2.5 ng/kg per minute on mean pulmonary artery pressure (MPAP) (top, A), cardiac output (CO) (middle, B), pulmonary vascular resistance (PVR) (C), and mixed venous oxygen saturation (SvO_2) (bottom, D) in 18 patients with pulmonary hypertension undergoing valvular heart surgery. The mean ± standard deviation values at T1 to T4 repeated measurement time settings have been compared.

RESULTS

The mean age of the 18 patients was 51.05 ± 12.05 years and ranged from 25 to 71 years old. Group 1 and group 2 have been compared. Bypass time was 84 ± 13.74 minutes and cross-clamp time was 53.6 ± 6.5 minutes for group 1; for group 2, bypass time was 98 ± 11.74 minutes and cross-clamp time was 68 ± 7.74 minutes. The duration of surgery was 256 ± 22.24 minutes for group 1 and 271 ± 25.33 minutes for group 2. All patients survived after surgery, were extubated in ICU, and were discharged within 5 days. The study protocol did not continue in the postoperative period. Patients were weaned from iloprost and nitroglycerin depending on their status in the intensive care unit. The hemodynamic data are given in Table 2. The hemodynamic parameters have been evaluated before incision (T1), 10 minutes after chest opening (T2), and 5 minutes and 20 minutes after CPB (T3 and T4).

The results have been summarized in Table 2 and the Figure. Before bypass, evaluation of T1 and T2 measurements shows that for group 1 (at a dosage of 0.5 to 1 µg/kg per minute) MPAP was reduced from 27.90 ± 4.75 to 21.10 ± 3.90 mmHg and PVR was reduced from 195.50 ± 60.72 to 130 ± 42.78 dyn sec cm –5 (*P* values <.05 have been considered statistically significant for all analyses). On the other hand, group 2 (at a dosage of 1.25 to 2.5 ng/kg per minute) MPAP was reduced from 33.00 ± 6.76 to 22.38 ± 5.45 mmHg and PVR was reduced from 282.50 ± 99.06 to 117 ± 53.32 dyn sec cm –5. The statistical analysis demonstrates that for group 2, both MPAP and PVR reductions were more pronounced. Although mean arterial pressure (MAP) and systemic vascular resistance (SVR) showed decreases in measurements from T1 to T4, heart rate (HR) increased in the data from T1 to T4 (for MAP, SVR, and HR, *P*-repeated measurements indicate *P* <.05 as statistically significant). Iloprost caused a significant increase in CO (from 4.24 ± 1.02 to 5.03 ± 0.98 L/min) compared to nitroglycerin (from 4.91 ± 0.62 to 5.01 ± 0.55 L/min). Pulmonary capillary wedge pressure (PCWP) decrease was more pronounced in group 2 (from 18.50 ± 3.63 to 14.13 ± 2.85 mmHg) and statistically different than group 1 (from 15.20 ± 2.86 to 13.20 ± 1.93 mmHg).

In the T3 and T4 measurements, the analysis of hemodynamic parameters showed similar results. Inotropic support of dobutamin was started at the end of the bypass period, as shown in Table 2. In group 1 (at a dosage of 0.5 to 1 µg/kg

Table 3. Comparison of the Plasma Nitric Oxide Measurements Obtained From Pulmonary Mixed Venous Blood at T1 and T4 Measurements (Median Values)*

	P Group	*P*-Repeated	T1, μM/mL	T4, μM/mL
Group 1	.0001	.005	13.8	34.2
Group 2		.017	38.43	26.1

*For *P* and *P*-repeated measurements *P* <.05. The plasma nitric oxide levels of group 1 were calculated (median) at 38.43 for T1 and at 26.1 μM/mL for T4, for group 2 the levels were calculated at 13.8 μM/mL and 34.2 μM/mL, respectively. The *P* value for group 1 was .005, for group 2 it was .017, and between groups it was .0001.

per minute), MPAP was reduced from 23.20 ± 5.20 to 18.50 ± 5.10 mmHg and PVR from 160.80 ± 39.76 to 137.40 ± 56.54 dyn sec cm –5. On the other hand, group 2 (at a dosage of 1.25 to 2.5 ng/kg per minute) MPAP was reduced from 23.20 ± 5.20 to 18.50 ± 5.10 mmHg and PVR was reduced from 160.80 ± 39.76 to 137.40 ± 56.54 dyn sec cm –5. Although MAP and SVR showed a decrease in the measurements from T1 to T4, HR provides an increase in the data from T1 to T4 (*P* <.05). Iloprost causes significant increase in CO (from 4.91 ± 0.91 L/min to 5.49 ± 0.91 L/min) compared to the nitroglycerin group (from 5.23 ± 0.80 L/min to 5.27 ± 0.74 L/min). PCWP decrease was statistically different between the iloprost group (from 16.50 ± 2.33 mmHg to 13.50 ± 2.07 mmHg) and the nitroglycerin group (14.80 ± 4.02 mmHg to 11.40 ± 2.95 mmHg).

In the T1 and T2 measurements, iloprost improved the oxygenation by raising the mixed venous oxygen saturation (from 76.53% ± 5.59% to 81% ± 4.84%) compared to nitroglycerin (75.90% ± 4.23% to 75.30% ± 4%). After the bypass (T3 and T4), the increase in oxygenation values was higher in group 2 (from 76.40% ± 4.07% to 85.00% ± 4.66%) than in group 1 (from 75.70% ± 5.35% to 76.10% ± 5.61%). The comparison of mixed venous oxygen saturation shows high mixed venous oxygen saturation values for both groups that may result from use of 100% O_2 during surgery and the lack of oxygen by the peripheral tissue due to hypothermia and vasoconstriction. The mixed venous oxygen saturation values are high in this study and may not demonstrate healthy measurement values. The values were higher for group 2 and the significance of this result needs further investigation (Figure).

In Table 3, the plasma nitric oxide levels that were obtained from pulmonary mixed venous blood have been compared to demonstrate the difference in the action mechanism of these drugs. In group 2, there has been no increase in the levels of nitric oxide (NO-2 and NO-3) from T1 to T4 (median, 38.43 to 26.1 μM/mL), and there is a clear increase in the levels of nitric oxide in group 1 (median, 13.8 to 34.2 μM/mL). The *P* value for group 1 was .005, and for group 2 it was .017.

DISCUSSION

The cause of pulmonary hypertension after CPB is probably a combination of pre-existing pulmonary hypertension exacerbated by CPB-induced damage to the pulmonary artery endothelium and further loss of vasodilator function. Pulmonary hypertension may produce acute RV failure and an inadequate CO. Most intravenous agents that dilate the pulmonary vasculature, such as milrinone, dobutamine, nitroglycerin, sodium nitroprusside, and the calcium channel antagonists, are prone to cause systemic hypotension that will decrease coronary perfusion to the right ventricle [Cockrill 2001].

Nitroglycerin is an intravenous drug commonly used to treat pulmonary hypertension. The use of intravenous nitrovasodilators is, however, often limited by systemic effects. Nitroglycerin increases venous admixture, which normally results in a decrease in arterial oxygen tension. The hemodynamic effects of intravenous nitroglycerin have been investigated. Left ventricular end-diastolic pressure was reduced most rapidly, but the systolic blood pressure was not affected by nitroglycerin [Curry 1993]. In humans, nitroglycerin was reported to reduce pulmonary artery pressure and PVR without eliciting much systemic arterial vasodilation [Palevsky 1997]. At low doses it shows venodilator effects, whereas at high doses it acts as an arterial dilator. There is a MAP decrease and an HR increase after nitroglycerin doses in this study, but it is not significantly different from the iloprost doses (Table 2 and Figure).

Prostacyclin and iloprost are other drugs that have been used in the treatment of primary or secondary pulmonary hypertension in the intravenous form. Because iloprost and nitroglycerin act by different pathways they can be used together to increase pulmonary vascular dilatation. The appropriate dosage and comparison of the hemodynamic data and possible side effects of the combined usage of these drugs should be investigated in another study. In this study, the nitroglycerin group significantly increased the NO levels but the iloprost group did not show a similar effect (Table 3).

In this study, good data was found for hemodynamic changes after intraoperative use of iloprost during repeated measurements of T1 to T4. Iloprost acts very quickly via intravenous use. The data have to be followed in the intensive care unit to provide data for continuation of iloprost use in this setting. Sudden interruption of the use of iloprost may cause rebound hypertension. There is a need for larger group studies in valvular replacement surgeries to determine any side effects.

Continuous intravenous infusion of prostacyclin or iloprost has proven to have beneficial effects on hemodynamics, exercise capacity, and survival in patients with primary pulmonary hypertension [Higgenbottam 1998]. In a recent study by Opitz et al, the hemodynamic response of prostacyclin and iloprost (aerosolized and intravenous) in primary pulmonary hypertension were compared. Intravenous prostacyclin (7.2 ± 3.4 ng/kg per minute) and iloprost (1.2 ± 0.5 ng/kg per minute) both reduced pulmonary vascular resistance and SVR and arterial blood pressure, and CO increased. The study also provides data for inhaled iloprost and supports that it has no systemic effect compared to iloprost [Opitz 2003]. There is also an animal study by Kisch-Wedel et al, in which the investigators demonstrated that intravenous iloprost and epoprostenol increased left ventricular contractility in vivo whereas intravenous sodium nitroprusside and adenosine did not [Kisch-Wedel 2003]. In our study, intravenous iloprost at a dosage of 1.25 to 2.5 ng/kg per minute reduced MPAP and PVR. In addition, although MAP and SVR were also

reduced, HR was increased (Table 2 and Figure). Also, after CPB there is administration of an inotropic agent that contributes to this change. In both groups, an inotropic agent has been used. Iloprost causes significant increase in CO compared to nitroglycerin. In this study, the results support that intravenous iloprost can be effectively used in the treatment of pulmonary hypertension during valve surgery and especially after CPB to prevent impending RHF.

Adequate treatment of RV failure consists of different strategies. The main goal is to decrease RV afterload by using vasodilating agents [Naeije 2001]. During cardiac surgery, severe pulmonary hypertension requires adequate and prompt treatment, and successful use of inhaled iloprost administration was presented in a few recent case reports [Schroeder 2000; Lowson 2002; Rex 2003]. Schroeder et al present 5 patients that underwent coronary artery bypass graft surgery and received inhaled PGI_2 to treat pulmonary hypertension and RV failure [Schroeder 2000]. Patients showed a mean 35% decrease in PVR and a mean 26% increase in cardiac index (CI). There was a small but significant 7% decrease in MPAP and 23% in SVR. Lowson and Schroeder et al demonstrated the use of inhaled prostacyclin for the treatment of pulmonary hypertension after RV failure during cardiac surgery [Schroeder 2000; Lowson 2002]. In these studies, the use of inhaled iloprost as a rescue medication was shown, whereas Rex at al included inhaled iloprost during weaning from bypass before RV failure occurs [Rex 2003]. In our study, we used intravenous iloprost as an integral part of the treatment of pulmonary hypertension before and after CPB during valve surgery operation. The appropriate dosing of iloprost or nitroglycerin provides an adequate response to lower MPAP and PVR with acceptable hemodynamic parameters during the surgery. All patients survived after surgery, were extubated in ICU, and were discharged within 5 days.

Inhaled iloprost use has been reported to have several advantages, including pulmonary vasodilatation without systemic side effects [Leuchte 2004; Olschewski 2004]. There are several drawbacks to the use of inhaled iloprost. The precise dosing and clinical administration is difficult. In the literature, various methods and dosing schedules are described [Hoeper 2000; Olschewski 2002; Hallioglu 2003]. The clinical response is dose-dependent with an apparent ceiling effect. The hemodynamic effect of inhaled iloprost levels off within 30 to 90 minutes. It has been demonstrated in several studies to result in a decrease in PAP and PVR and an increase in CO [Hoeper 2000; Olschewski 2002] compared to intravenous nitroglycerin, which shows significant decrease in MPAP, PVR, MAP, and SVR, but no significant increase in CO [Curry 1993].

In this study, iloprost has been effectively used without any side effects. The reported side effects of intravenous iloprost are diarrhea and systemic vasodilatation-related flushing, headaches, jaw pain, and hypotension [Badesch 2000]. Intravenous administration of medications increases the risk of line sepsis and there are reports of accidental interruption of intravenous prostacyclin, causing rebound pulmonary hypertension [Higgenbottam 1998]. Skin rash and elevation in liver enzymes have also been reported. We did not observe any of these side effects. The recent study by Opitz et al provides the same results of no significant systemic side effects with the appropriate dosage and use of intravenous prostacyclin and iloprost [Opitz 2003].

Badesch et al have presented a study of 111 patients with pulmonary hypertension secondary to the scleroderma spectrum of disease and have shown that continuous epoprostenol therapy improves exercise capacity and cardiopulmonary hemodynamics [Badesch 2000]. Higgenbottam et al have demonstrated that both intravenous PGI_2 and iloprost improve exercise tolerance and prolong survival in patients showing RV failure [Higgenbottam 1998]. Strong predictors of survival in these patients were reported as NYHA grade, CI, PVR, and SvO_2. In our study, with intravenous iloprost administration there is a statistically significant rise in SvO_2 compared to the intravenous nitroglycerin group. Despite the limitations of our study, this finding provides an important reason to perform further studies in larger groups and to have follow-up series that investigate the relation of intravenous iloprost to better survival rates after valvular heart surgery.

Inhaled iloprost use has recently been extensively investigated in several large group studies for treatment of severe pulmonary hypertension [Hoeper 2000; Olschewski 2002]. There is a reduction in MPAP and a significant increase in CI. These studies demonstrate that inhaled iloprost is a good agent that can be used in severe pulmonary hypertension. There are reports of difficulties in appropriate dosing and administration of inhaled iloprost. There is need for 6 to 8 applications of iloprost with possible rebound pulmonary hypertension in between the applications.

CONCLUSION

During the valvular heart surgery, in which acute management of pulmonary hypertension is crucial to prevent development of RV failure, the easy administration of intravenous iloprost with appropriate dosing can be a safe alternative to intravenous nitroglycerin or inhaled iloprost. In this administration, the titration of dosing is easier and more precise than with inhaled iloprost. Intravenous iloprost has a more pronounced reduction in MPAP and PVR and increase in CO compared to intravenous nitroglycerin at appropriate administration doses. During operations where abrupt management of pulmonary hypertension is required, systemic use of iloprost or nitroglycerin at appropriate doses via pulmonary artery catheter offers adequate relief of hypertension and is well tolerated without any significant adverse effects. The plasma nitric oxide levels do not rise when iloprost is used. Because iloprost and nitroglycerin act via different mechanisms they can be used together at appropriate doses to demonstrate additive effects on the relief of pulmonary hypertension. Larger group studies will provide data for the better titration of dosing to preserve hemodynamic stability and to prevent possible systemic side effects.

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