Inhaled epoprostenol (prostacyclin) and pulmonary hypertension before cardiac surgery

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Objective: Pulmonary hypertension is commonly found in patients undergoing valvular surgery and can be worsened by cardiopulmonary bypass. Inhaled epoprostenol (prostacyclin) has been used for the treatment of pulmonary hypertension, but its effects compared with those of placebo on hemodynamics, oxygenation, echocardiographic examination, and platelet function have not been studied during cardiac surgery.

Methods: Twenty patients with pulmonary hypertension undergoing cardiac surgery were randomized in a double-blind study to receive inhaled epoprostenol (60 μg) or placebo. The inhalation occurred after induction of anesthesia and before surgical incision. The effects on left and right systolic and diastolic cardiac functions evaluated by means of pulmonary artery catheterization and transesophageal echocardiography, as well as oxygenation and platelet aggregation, were studied.

Results: Inhalation of epoprostenol significantly reduced indexed right ventricular stroke work from 10.7 ± 4.57 g · m · m^{-2} to 7.8 ± 3.94 g · m · m^{-2} ($P = .003$) and systolic pulmonary artery pressure from 48.4 ± 18 mm Hg to 38.9 ± 11.9 mm Hg ($P = .002$). The effect was correlated with the severity of pulmonary hypertension ($r = 0.76$, $P = .01$) and was no longer apparent after 25 minutes. There was no significant effect on systemic arterial pressures, left ventricular function, arterial oxygenation, platelet aggregation, and surgical blood loss.

Conclusion: Inhaled epoprostenol reduces pulmonary pressure and improves right ventricular stroke work in patients with pulmonary hypertension undergoing cardiac surgery. A dose of 60 μg is hemodynamically safe, and its effect is completely reversed after 25 minutes. We did not observe any evidence of platelet dysfunction or an increase in surgical bleeding after administration of inhaled epoprostenol.

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Pulmonary hypertension (PH) is associated with an increase in morbidity and mortality in patients undergoing cardiac surgery.[1] Many drugs have been used in recent years to treat PH. Among these are vasodilators, including epoprostenol (prostacyclin; PGI_2). However, its intravenous administration is limited by systemic hypotension because of nonselective vasodilation and by hypoxemia through worsening of intrapulmonary shunt caused by inhibition of hypoxic pulmonary vasoconstriction.[2,3]

Inhaled PGI_2 appears to be a selective pulmonary vasodilator comparable with inhaled nitric oxide (iNO) but acting through cyclic adenosine monophosphate instead of cyclic guanosine monophosphate.[4,5] Its administration can be a simpler and less expensive alternative to iNO. Its half-life is 2 to 3 minutes, and at physiologic pH, it spontaneously hydrolyses to 6-ketoprostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$). Thus its effect remains localized to ventilated lung units, it can decrease pulmonary artery pressure (PAP) without causing systemic hypotension and im-

prove oxygenation by decreasing ventilation-perfusion mismatch.[5-8] Its effect on cardiac function when given by means of inhalation is controversial but it can increase cardiac output when given intravenously.[9,10]

Finally, a drawback of PGI_2 is that it has been reported to alter platelet function,[11] which could be hazardous during cardiac surgery.

We have previously reported our retrospective experience with the use of inhaled PGI_2.[12] However, so far no study has evaluated its effects in patients undergoing cardiac surgery and simultaneously on several important clinical variables, such as the magnitude of its hemodynamic effect and its consequences on echocardiographic indices of right ventricular (RV) and left ventricular (LV) systolic and diastolic functions, oxygenation, platelet function, and bleeding.

Methods

Population

After approval by the research and ethics committee and obtaining informed consent, 20 patients with PH undergoing cardiac surgery with cardiopulmonary bypass were included in the study. Patients were considered to have PH if systolic pulmonary artery pressure (sPAP) was greater than 30 mm Hg or mean pulmonary artery pressure was greater than 25 mm Hg, as measured during the preoperative period or estimated by using Doppler echocardiography.[13] This was confirmed after insertion of a pulmonary artery catheter and before induction of general anesthesia. Patients with LV dysfunction (ejection fraction of <30%) or known bleeding diathesis were excluded. Further exclusion criteria were contraindications to transesophageal echocardiography (TEE), including esophageal disease or unstable cervical spine. A Parsonnet score was calculated for every patient.[1]

Protocol

Patients were premedicated with 1 to 2 mg of lorazepam administered orally 1 hour before the operation, as well as 0.1 mg/kg morphine administered intramuscularly and 0.2 to 0.4 mg of scopolamine administered intramuscularly before being taken to the operating room. In the operating room additional midazolam was added (0.01-0.05 mg/kg administered intravenously) as needed for patient comfort. Usual monitoring was installed, including a 5-lead electrocardiogram, pulse oximeter, peripheral venous line, radial arterial line, 15-cm 3-lumen catheter (CS-12703, Arrow International Inc, Reading, Calif), and fast-response thermodilution pulmonary artery catheter (Swan-Ganz catheter 7.5F; Baxter Healthcare Corporation, Irvine, Calif). Anesthesia was induced with 0.04 mg/kg midazolam and 1 μg/kg sufentanil, and muscle relaxation was achieved with 0.1 mg/kg pancuronium. After tracheal intubation, anesthesia was maintained with 1 $\mu g \times kg^{-1} \times h^{-1}$ sufentanil and 0.04 $mg \times kg^{-1} \times h^{-1}$ midazolam. No anesthetic gases were used. Minute ventilation was adjusted to maintain end-tidal carbon dioxide between 30 and 40 mm Hg with an infrared carbon dioxide analyzer. A 5.0-MHz TEE omniplane probe (Hewlett-Packard Sonos 5500, Andover, Mass) was inserted after induction of general anesthesia.

Drug Administration Protocol

Patients were equally divided into 2 groups to receive either inhaled PGI_2 or placebo in a double-blind randomized manner by using a computer-generated randomization table. Epoprostenol (Flolan; Glaxo-Wellcome Inc, Mississauga, Ontario, Canada) was given as epoprostenol 1.5 mg of salt dissolved in sterile glycine buffer diluent, for a concentration of 15 μg/mL. Each patient received 4 mL of a solution containing either PGI_2 or normal saline solution (placebo).

The study drug was administered through a jet nebulizer (Ref 8901; Salter Labs, Arvin, Calif) attached to the inspiratory limb of the ventilator near the endotracheal tube. Nebulization was achieved with a bypass flow of oxygen at 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 less than 30 cm H_2O and a normal end-tidal carbon dioxide.

Measurements

Hemodynamic parameters included central venous pressure, PAP, and pulmonary artery occlusion pressure. Cardiac output was assessed by using the thermodilution technique with 3 injections of room temperature dextrose 5% (10 mL) at end expiration. Systemic vascular resistances, pulmonary vascular resistances, RV stroke work, and LV stroke work were calculated by using a standard formula. Hemodynamic values were indexed for patient body surface area.

Arterial and mixed venous blood gases were obtained to measure pH, Po_2, Pco_2, HCO_3^-, and SO_2.

TEE examination was performed to evaluate systolic and diastolic parameters of LV and RV performance. The TEE examination included a midesophageal 4-chamber view, a short-axis transgastric view at the midpapillary level, and color flow Doppler imaging of the mitral valve to detect any unsuspected significant mitral valvulopathy. We first obtained a baseline transgastric short-axis view of the left ventricle at the midpapillary level, followed by a pulsed Doppler examination of pulmonary venous flow, transmitral flow, transtricuspid flow, and hepatic venous flow. The Doppler sample volume (2-mm width) was positioned in the left upper pulmonary vein approximately 1 cm proximal to its entrance into the left atrium to measure pulmonary venous flow by using color Doppler flow to sample maximal flow. When necessary, to minimize the angle between the Doppler beam and the pulmonary vein's long axis, we rotated the omniplane probe as far as needed from the horizontal plane. This axis was maintained throughout the examination. The same approach was used for hepatic venous flow. Mitral and tricuspid inflow velocities were measured at the tip of the atrioventricular valve leaflets. Three signals were obtained, and the maximal value was computed for analysis.[14] Two independent observers were involved: the first one recorded hemodynamic parameters, and the other, blinded to the hemodynamic data and to the study drug, simultaneously recorded the pulsed Doppler and 2-dimensional echocardiographic images. All TEE examinations were performed by anesthesiologists who were not in charge of the patient. After data recording, a third anesthesiologist blinded to all data reviewed the recorded sequence. All 2-dimensional images in which the LV and RV endocardial border could not be traced adequately by using Schnittger criteria, in

TABLE 1. Demographic data of the study population

	n	Epoprostenol	n	Placebo	*P* value
Age, y	10	65 ± 11	10	58 ± 12	.22
Sex					
Male	5	50%	4	40%	1
Female	5	50%	6	60%	
Weight, kg	10	76 ± 17	10	70 ± 20	.56
Height, m	10	1.65 ± 0.11	10	1.63 ± 0.08	.65
Parsonnet score	10	29.2 ± 6.5	10	32.4 ± 10.2	.4
Reoperation	3	30%	5	50%	.65
Aspirin use	0	0%	3	30%	.21
Preoperative heparin	3	30%	3	30%	1

which 80% of the endocardial contour has to be visualized, were excluded.[15] In addition, the Doppler signals were reviewed and rejected if they were not laminar and when a clear contour could not be determined for quantification of the velocity-time integral. Severe mitral stenosis or regurgitation were exclusion criteria for the measurement of mitral inflow. All the anesthesiologists performing the TEE measurements were board certified in perioperative TEE. If disagreement occurred between 2 reviewers, a third echocardiographer was asked to review the echocardiographic sequence. Our experience and interobserver variability in the measurement of systolic and diastolic function has been published previously.[16,17]

Platelet aggregation studies were performed on whole blood by using a Chronolog 560 whole blood lumi-aggregometer (Chronolog Corp, Havertown, Pa). Sodium citrate, 0.5 mL of a 3.2% solution, was added to 4.5 mL of venous blood. The citrated blood was diluted 1:1 with normal saline solution. After the solution had been cooled to 20°C to 25°C, a 900-μL sample was placed in a cuvette containing a silicone stir bar. After 3 minutes, 100 μL of chrono-lume (luciferase luciferon reagent, Chronolog Corp) was added. After another 2 minutes, 2 mmol/L of adenosine triphosphate (ATP) was added. The ATP standard was then measured for each patient. Two minutes later, an aggregant was added (20 μmol/L adenosine diphosphate, 5 μg/mL collagen, or 1 nmol/L arachidonic acid), and platelet aggregation and ATP release (luminescence) were measured. Blood loss was measured for the intraoperative period, as well as for the first 24 hours postoperatively.

Hemodynamic parameters were measured before (T1) and 10 minutes after (T2) induction of anesthesia, after nebulization of PGI_2 or placebo (T3), and 15 (T4) and 25 (T5) minutes after nebulization. Arterial and mixed venous blood gases were obtained at the same times, except for T5. TEE examination and platelet aggregation studies were performed before and after administration of PGI_2 or placebo. Patients were observed until discharge from the intensive care unit.

Statistical Analysis

Population size was calculated for a power of 80% and an α error of .05, assuming an sPAP of 40 ± 4 mm Hg to decrease by 20% in the PGI_2 group and remain stable in the placebo group.

Continuous variables were analyzed with the Student *t* test and categoric variables with the χ^2 or Fisher exact test. Two-factor (time and group) repeated-measures analysis of variance was used to determine time variations between the 2 groups. In case of significant interaction, time × group comparison was performed with Bonferroni corrections.

The Pearson correlation test was performed to determine the relationship between the level of sPAP and the degree of reduction of sPAP after PGI_2 and placebo administration.

Results

Twenty-seven patients were enrolled in the study. Four were later not randomized because they failed to meet the inclusion criteria for PH on arrival to the operating room. Two were excluded because the operation was subsequently rescheduled and another because of agitation. Demographic variables were similar in both groups (Table 1).

Hemodynamics

Baseline hemodynamic variables were similar between the 2 groups (Table 2). Baseline sPAP was 61.2 ± 19 mm Hg in the PGI_2 group and 54.3 ± 14.6 mm Hg in the placebo group ($P = .4$). These decreased significantly after induction of anesthesia in both groups to 48.4 ± 18 mm Hg and 42.7 ± 12.8 mm Hg, respectively. After administration of the study drug, a decrease was noted in the PGI_2 group to 38.9 ± 11.9 mm Hg ($P = .002$), as opposed to that seen in the placebo group. Fifteen minutes after the end of nebulization, these values were stable (42 ± 12.4 vs 43.6 ± 12.5 mm Hg). After 25 minutes, they returned to baseline in the PGI_2 group to 53.3 ± 17.6 mm Hg and remained stable in the placebo group at 43.5 ± 13 mm Hg (Figure 1). There was a significant positive correlation between the severity of PH before the administration of inhaled PGI_2 and the magnitude of the decrease in sPAP ($r = 0.76$, $P = .01$). Heart rate decreased in the PGI_2 group from 64.4 ± 8.8 to 58.5 ± 11 beats/min ($P = .002$). It stayed stable thereafter until 25 minutes after inhaled PGI_2, when it increased to 62.8 ± 11.6 beats/min ($P = .001$). Mean PAP did not change significantly after PGI_2 administration nor did systemic arterial pressures. Cardiac indexes remained unchanged throughout the study. Compared with placebo, indexed RV stroke work decreased after PGI_2 inhalation from 10.7 ± 4.57 to 7.8 ± 3.94 $g \cdot m \cdot m^{-2}$ ($P = .003$) and remained stable thereafter for 25 minutes.

Oxygenation

Oxygenation data are given in Table 3. The Pao_2 value at baseline was significantly different on arrival in the operating room with a nasal cannula at 4 L/min of oxygen (173.1 ± 65.2 mm Hg in the PGI_2 group vs 251.5 ± 95.4 mm Hg in the placebo group, $P = .05$), but this difference disappeared after induction of anesthesia with a fraction of inspired oxygen of 100% (428.2 ± 65.2 vs 443.7 ± 64.9, respectively; $P = .6$). Otherwise, oxygenation variables did not change throughout the study.

TABLE 2. Hemodynamic variations of the population throughout the study

	T1	T2	T3	T4	T5
Epoprostenol					
HR (beats/min)	66.1 ± 9.7	64.4 ± 8.8	58.5 ± 11*	56.7 ± 10.6	62.8 ± 11.6†
SAP (mm Hg)	134.4 ± 28.6	105.3 ± 15	101.2 ± 19.3	108.6 ± 22	124.9 ± 28
MAP (mm Hg)	85.9 ± 14.6	67.9 ± 11.5	63.8 ± 10.5	69.7 ± 13.7	82.6 ± 19
CVP (mm Hg)	11.1 ± 6.8	11 ± 4.9	10.8 ± 4.8	11.5 ± 4.9	13.3 ± 4.3
PAOP (mm Hg)	22.8 ± 8.1	21.8 ± 6.6	19 ± 6.4	20.6 ± 6.6	24.6 ± 9
sPAP (mm Hg)	61.2 ± 19	48.4 ± 18§	38.9 ± 11.9¶	42 ± 12.4	53.3 ± 17.6‖
MPAP (mm Hg)	41.5 ± 9	32.9 ± 9.2§	28.2 ± 8.2	30.4 ± 8.4	36 ± 11.1‖
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.5 ± 0.7	2.2 ± 0.6	2 ± 0.5	2 ± 0.6	1.9 ± 0.5
EV ($mL \cdot beat^{-1} \cdot m^{-2}$)	69.4 ± 20	65.4 ± 17.3	62.9 ± 17.6	66 ± 19.2	56.7 ± 17.7
SVRI ($dyne \cdot s \cdot cm^{-5}$)	2474 ± 424.2	2078 ± 566.6	2260 ± 381.3	2460 ± 719.7	3157 ± 1249
PVRI ($dyne \cdot s \cdot cm^{-5}$)	683.5 ± 449.1	451.7 ± 315.6	404.9 ± 250	398.2 ± 266.6	555.4 ± 347.3
LVSWI ($g \cdot m \cdot m^{-2}$)	33.1 ± 16.1	21.7 ± 8.6	22.5 ± 10.8	24.3 ± 11.6	24.6 ± 12.3
RVSWI ($g \cdot m \cdot m^{-2}$)	15.5 ± 6.3	10.7 ± 4.6§	7.8 ± 3.9#	8.3 ± 4.2	8.6 ± 3.1
Placebo					
HR (beats/min)	67.8 ± 12.5	68.5 ± 14.4	65.5 ± 16	61.4 ± 14.8	61.5 ± 11.7
SAP (mm Hg)	142.2 ± 26.4	118.4 ± 24.1	119.6 ± 23.1	117.4 ± 24.6	119.1 ± 22.1
MAP (mm Hg)	92 ± 14.2	77.3 ± 13.6	78.4 ± 14.3	76.7 ± 16.1	78.6 ± 11
CVP (mm Hg)	14.4 ± 7.1	11.3 ± 5.2‡	11.7 ± 4.7	12.6 ± 4.1	12.9 ± 4.6
PAOP (mm Hg)	21.7 ± 11.3	19.7 ± 8	19.9 ± 8.4	21.1 ± 6.5	21.1 ± 5.8
sPAP (mm Hg)	54.3 ± 14.6	42.7 ± 12.8‡	41.3 ± 15.2	43.6 ± 12.5	43.5 ± 13
MPAP (mm Hg)	38.4 ± 9.9	30 ± 9.6‡	29.6 ± 13.4	30.4 ± 9.1	29.6 ± 7.6
CI (($L \cdot min^{-1} \cdot m^{-2}$)	2.8 ± 0.8	2.7 ± 0.8	2.5 ± 0.7	2.4 ± 0.7	2.2 ± 0.6
EV ($mL \cdot beat^{-1} \cdot m^{-2}$)	73.2 ± 15.7	67.7 ± 18.9	68.5 ± 20.2	68.1 ± 18.5	63.6 ± 15.4
SVRI ($dyne \cdot s \cdot cm^{-5}$)	2282 ± 635.2	2128 ± 708.3	2290 ± 776.4	2497 ± 786.8	2492 ± 924.3
PVRI ($dyne \cdot s \cdot cm^{-5}$)	521.7 ± 310	311.8 ± 147.1	299.5 ± 161.8	352.9 ± 208.6	324.5 ± 276.7
LVSWI ($g \cdot m \cdot m^{-2}$)	40.4 ± 18.4	30.3 ± 11.7	31 ± 9.6	32 ± 11.9	27.2 ± 6.6
RVSWI ($g \cdot m \cdot m^{-2}$)	13.4 ± 6.2	9.5 ± 4.9‡	8.8 ± 5	9.5 ± 5	7.8 ± 3.9

HR, Heart rate; *SAP*, systemic arterial pressure; *MAP*, mean arterial pressure; *CVP*, central venous pressure; *PAOP*, pulmonary artery occlusion pressure; *MPAP*, mean pulmonary arterial pressure; *CI*, cardiac index; *EV*, ejection volume; *SVRI*, systemic vascular resistance index; *PVRI*, pulmonary vascular resistance index; *LVSWI*, LV stroke work index; *RVSWI*, RV stroke work index.
*$P = .002$ T2 to T3 in prostacyclin group.
†$P = .001$ T4 to T5 in prostacyclin group.
‡$P < .001$ T1 to T2 in placebo group.
§$P < .001$ T1 to T2 in prostacyclin group.
‖$P < .001$ T3 to T5 in prostacyclin group.
¶$P = .002$ T2 to T3 in prostacyclin group.
#$P = .003$ T2 to T3 in prostacyclin group.

CSP

Echocardiography

Echocardiography data are given in Table 4. Of 240 images taken, 43 were rejected according to the predefined criteria. There was a 3% interobserver discordance. TEE examinations were similar in both groups before and after inhalation of PGI_2 or placebo, but in the PGI_2 group a tendency toward improved fractional area change or systolic function was noted for both the left and right ventricles. Also, in the PGI_2 group the systolic portion of hepatic flow tended to increase, and the diastolic portion remained stable compared with that seen with placebo, which suggests improvement in RV diastolic function, but this did not reach statistical significance.

Platelet Aggregation

Platelet aggregation data are shown in Table 5. Platelet aggregation studies showed a significant difference in platelet luminescence produced by collagen (0.8 ± 0.2 nm in the PGI_2 group vs 1.2 ± 0.5 nm in the placebo group, $P = .046$), but this difference remained stable throughout the study (0.7 ± 0.3 vs 1.1 ± 0.5 nm, respectively; $P = .055$).

Otherwise, platelet aggregation studies showed no difference between the 2 groups with either adenosine diphosphate, collagen, or arachidonic acid used as aggregants. Surgical blood loss was similar in both groups for both the intraoperative and postoperative periods.

Discussion

This is the first randomized controlled trial to examine hemodynamic, echocardiographic, oxygenation, and platelet function effects of inhaled PGI_2 versus placebo in patients after anesthesia induction and before cardiac surgery. It confirms that inhaled PGI_2 can be a selective pulmonary vasodilator and decrease indexed RV stroke work. Our TEE

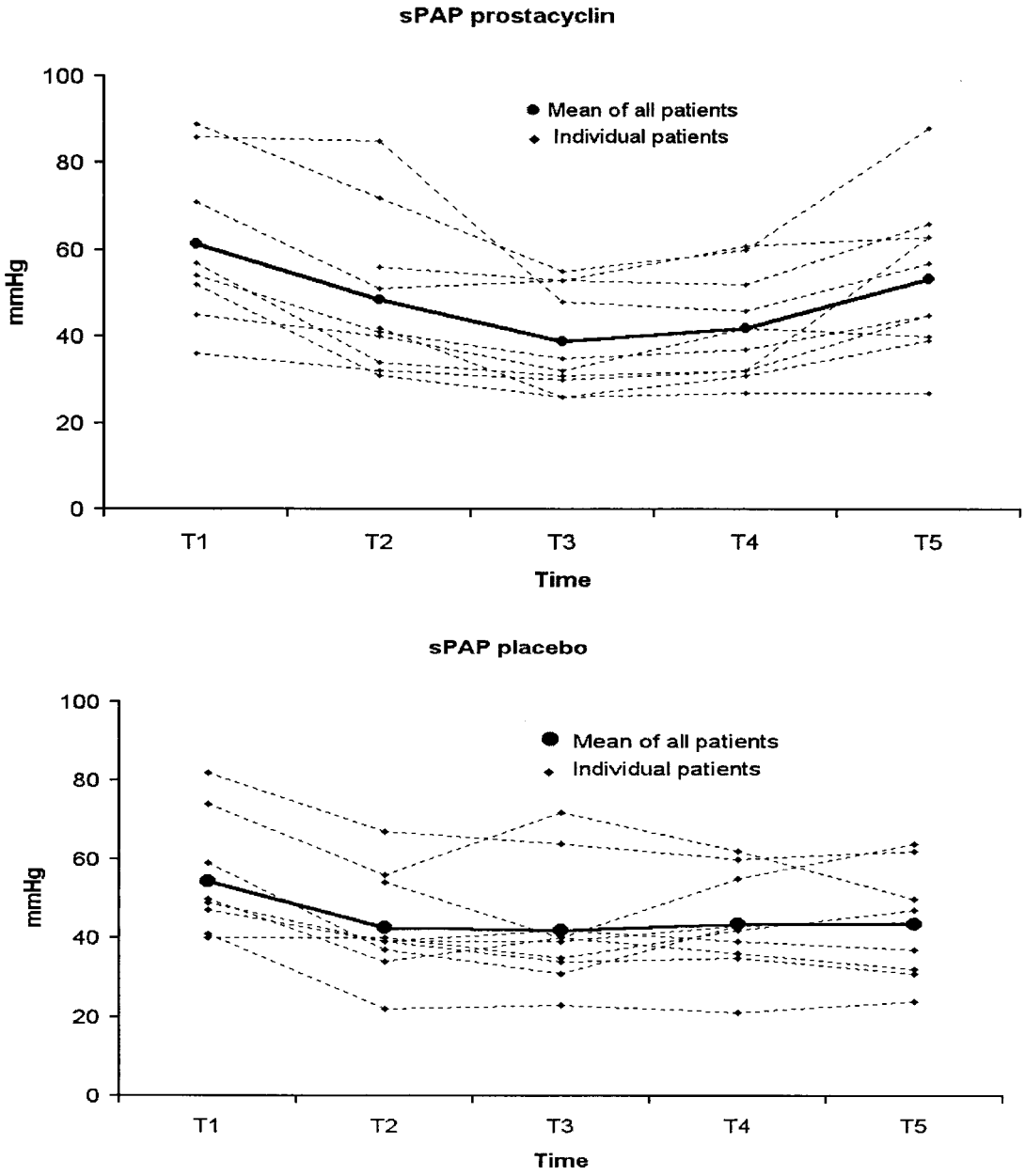

Figure 1. sPAP variations of each patient before (T1) and 10 minutes after (T2) induction of anesthesia, after nebulization of PGI_2 or placebo (T3), and 15 (T4) and 25 (T5) minutes after nebulization.

findings also suggest a tendency toward improvement of both RV and LV systolic functions, as well as RV diastolic function. The dose administered was safe, with no systemic hypotension or any effect on platelet aggregation.

Inhaled PGI_2 decreases PAP. This has been confirmed in many animal[18-20] and human[12,21-24] studies. Because of this, it reduces RV afterload and can improve RV systolic and diastolic functions. In dogs having PH after hypoxic pulmonary vasoconstriction, Zwissler and colleagues[21] demonstrated improvement of RV contraction indices through reduction in RV afterload with a small dose of inhaled PGI_2. In human subjects one study showed improvement of RV ejection fraction in patients having PH caused by pulmonary fibrosis.[23] Haraldsson and colleagues[25] showed improvement of RV performance with inhaled PGI_2 in patients having PH after cardiac surgery. Our study demonstrates a reduction in indexed RV stroke work in patients before cardiac surgery. The reduction in RV stroke work index was

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