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Inhaled prostacyclin and platelet function after cardiac surgery and cardiopulmonary bypass

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Abstract *Objective:* To study the effects of 6 h inhalation of aerosolized prostacyclin (PGI_2) on platelet function.
Design: In a prospective, double-blind, randomized study, 28 patients scheduled for elective cardiac surgery requiring cardiopulmonary bypass (CPB), received either 0.9 % sodium chloride ($n = 8$), PGI_2 5 $\mu g \times ml^{-1}$ ($n = 10$) or PGI_2 10 $\mu g \times ml^{-1}$ ($n = 10$) as an aerosol for 6 h postoperatively.
Setting: Cardiothoracic intensive care unit at a university hospital.
Interventions: All patients were studied immediately after surgery during mechanical ventilation and sedation. The PGI_2 solutions or saline were administered with a jet nebulizer.
Measurements and results: Bleeding time and chest tube drainage were measured. Blood samples for platelet aggregation, thrombelastography (TEG) and analysis of coagulation parameters and the stable prostacyclin metabolite 6-keto-$PGF_1\alpha$ were obtained immediately before inhalation and after 2, 4 and 6 h of inhalation. After 6 h of PGI_2 inhalation, regardless of administered dose, there was a lower rate of platelet aggregation and a lower maximal increase in light transmission in response to adenosine diphosphate (ADP) than in the control group. The TEG variable reaction time (R) was prolonged after 4 and 6 h of inhalation in the PGI_2 group receiving 10 $\mu g \times ml^{-1}$. There were no differences between groups with respect to bleeding time and chest tube drainage or any of the other variables examined.
Conclusion: Inhalation of PGI_2 for 6 h in patients after cardiac surgery is associated with impaired platelet aggregation detected by in vitro techniques, with no in vivo signs of platelet dysfunction.

Key words Aerosol · Prostacyclin · Platelet function · Cardiac surgery

Introduction

After cardiac surgery and orthotopic heart transplantation, elevated pulmonary vascular resistance (PVR) may cause right ventricular (RV) failure and premature death [1]. Vasodilator therapy is therefore often required to prevent or treat this condition [2]. Intravenous administration of potent vasodilators such as nitrates or prostaglandins is hampered, due to lack of selectivity for the pulmonary vasculature, by dose-dependent systemic vasodilation, resulting in hypotension and increased intrapulmonary shunt [2, 3, 4, 5].

The biomediator nitric oxide (NO) has, when inhaled, selective pulmonary vasodilatory properties without effects on the systemic vasculature [5, 6]. However, due to its potential toxicity, NO requires specialized delivery systems and monitoring [7]. There have also been reports indicating inhibition of platelet aggregation by inhaled NO, both in patients with acute respiratory distress syndrome (ARDS) and in healthy volunteers [8, 9].

Prostacyclin (PGI_2) is another biomediator synthesized by the vascular endothelium. It is a potent vasodilator with no known toxic effects and a half-life of 2–3 min [10]. Inhaled aerosolized PGI_2 is attracting increasing attention as a selective pulmonary vasodilator in various conditions associated with elevated PVR. Evidence has been presented of beneficial and pulmonary selective effects after cardiac surgery and heart transplantation [11], in patients with ARDS [12, 13, 14] as well as in neonates and adults with pulmonary hypertension of various origins [15, 16, 17, 18, 19].

Side effects of short-term inhalation of PGI_2, such as inhibition of adenosine diphosphate (ADP)-induced platelet aggregation in healthy volunteers as well as a slight accentuation of bronchospasm in asthmatic patients, have been reported by a few investigators [20, 21, 22]. During prolonged (8 h) PGI_2 inhalation in an animal setting, no effects on platelet aggregation or signs of acute pulmonary toxicity were demonstrated [23].

However, no clinical studies have been presented addressing the potential problem of impaired platelet function after long-term PGI_2 inhalation in patients undergoing surgery. This could increase the risk of intra- and postoperative bleeding, especially in connection with extracorporeal circulation with its well-known detrimental effects on platelet number and function. The present study was designed to investigate the effects of 6 h inhalation of aerosolized PGI_2 on the platelet function in patients after cardiac surgery requiring cardiopulmonary bypass (CPB).

Material and methods

Subjects

The study was performed at the Scandinavian Heart Center, Göteborg, Sweden, conducted according to the principles established in Helsinki and approved by the Human Ethics Committee of the Medical Faculty, University of Göteborg and the Swedish Medical Products Agency, Uppsala. Thirty consecutive adult patients scheduled for elective cardiac surgery requiring cardiopulmonary bypass were included in the study after informed consent.

Exclusion criteria

The exclusion criteria were continued preoperative anticoagulation therapy 7 days prior to surgery, history of coagulation abnormalities, pre-, intra- or postoperative transfusion of blood products, preoperative platelet count less then $100 \times 10^9 \times l^{-1}$, plasma activated partial thromboplastin time > 42 s, plasma prothrombin complex < 70 % and serum creatinine > 110 $\mu mol \times l^{-1}$.

Anesthesia and perioperative procedure

Preoperative medication consisted of intramuscular morphine 0.1 $mg \times kg^{-1}$, scopolamine 0.2–0.4 mg and oral diazepam 0.1 $mg \times kg^{-1}$. Anesthesia was induced with fentanyl 3–7.5 $\mu g \times kg^{-1}$, thiopentone 2–5 $mg \times kg^{-1}$ and pancuronium 0.1 $mg \times kg^{-1}$ and sustained with enflurane/isoflurane 0.5–2.0 % and additional fentanyl 0–2 $\mu g \times kg^{-1}$. Patients were initially ventilated with inspired 100 % oxygen adjusted to lower fractions after monitoring of arterial oxygen tension (PaO_2), hemoglobin oxygen saturation (SaO_2) and arterial carbon dioxide tension ($PaCO_2$) as well as end-expiratory carbon dioxide measurements. During cardiopulmonary bypass (CPB), propofol was administered, 0.05–0.1 $mg \times kg^{-1} \times min^{-1}$.

Cardiopulmonary bypass

After administration of intravenous porcine heparin chloride (300 $IU \times kg^{-1}$), aortic and venous cannulas were inserted. Systemic anticoagulation was verified by an activated clotting time (ACT) > 400 s (Hemachron Junior; International Technidyne, Edison, N.J., USA). CPB was conducted using a COBE DUO membrane lung oxygenator (COBE, Arvada, Colo., USA), and a nonpulsatile flow of 2.4 $l \times min^{-1} \times m^{-2}$. The circuit was primed with 1500 ml balanced salt solution and 200 ml 15 % mannitol. In all patients, hypothermia (32–34 °C) and aortic cross-clamping with cold hyperkalemic cardioplegia were used during CPB. For pH management, α-stat methodology was used and activated clotting time (ACT) was maintained > 400 s. After the surgical procedure, patients were warmed to a bladder temperature of 36.5–37 °C. After weaning from CPB, blood remaining in the venous reservoir was reinfused. Anticoagulation was reversed with protamine sulphate, given at a ratio of 1 mg:100 IU heparin and its effect was verified with ACT < 110 s (low range test tube; Hemo Tec, Englewood, Colo., USA). After surgical hemostasis had been obtained, the chest was closed and patients were transported to the intensive care unit (ICU).

Experimental groups

The patients were treated in the ICU by the attending anesthesiologist according to postoperative routine, mechanically ventilated (Engström ventilator Erica/Elvira, Gambro Engström, Bromma, Sweden) throughout the study and continuously sedated with propofol (mean dose ± SEM: control group, 0.041 ± 0.003 $mg \times kg^{-1} \times min^{-1}$; PGI_2 5 $\mu g \times ml^{-1}$ group, 0.044 ± 0.003; PGI_2 10 $\mu g \times ml^{-1}$ group, 0.045 ± 0.003 $mg \times kg^{-1} \times min^{-1}$). After initial observation, patients were randomized in a double-blind manner to receive inhalation of aerosolized 0.9 % sodium chloride (NaCl)(control group, $n = 8$), aerosolized prostacyclin (PGI_2, epoprostenol; Flolan Glaxo Wellcome Laboratories, Beckenham, Kent, UK) at a concentration of 5 $\mu g \times ml^{-1}$ ($n = 10$) or 10 $\mu g \times ml^{-1}$ ($n = 10$) for the following 6 h. Two patients were excluded due to perioperative blood transfusions.

Measurements

Blood samples were obtained from the radial artery catheter for measurements of hematocrit, platelet count (H I, Bayer, Tarrytown, N.Y., USA), prothrombin complex, activated partial thromboplastin time (Thrombotimer, Benckh Electronic, Nordenstadt, Germany), platelet aggregation (see below), 6-keto-$PGF_1\alpha$ (see below), PaO_2, $PaCO_2$ as well as SaO_2. Blood samples for thrombelastography (TEG) were obtained from a separate central venous line used only for this purpose. A standardized (i.e. template) bleeding time was measured in the volar aspect of the upper ex-

tremity using Simplate R (Organon Teknika, Durham, N. C., USA) [24]. Blood sampling, measurements and chest tube drainage recordings were performed before initiating inhalation (0 h) and after 2, 4 and 6 h of inhalation. At all arterial and central venous catheter sites, a non-heparinized flush solution was used.

Platelet aggregation

Arterial blood samples for platelet aggregation were collected in 0.1 vol of 0.13 M sodium citrate, allowed to enter the collecting tube spontaneously after initial gentle aspiration of 20 ml. Platelet-rich plasma (PRP) was prepared by centrifugation at 110 *g* for 10 min at room temperature. Platelet-poor plasma (PPP) was prepared by centrifugation of residual content, after PRP removal, at 2000 *g* for 10 min. All equipment used for the blood, PRP and PPP handling was plastic except for the aggregometer cuvettes, which were siliconized glass.

Measurement of aggregation was initiated within 20 min from blood sampling, by turbidometric method [25], using a dual channel platelet aggregometer (Payton Associated, Ontario, Canada) and the curves were recorded on a paper chart recorder at a speed of 2 cm × min^{-1}. The light transmission was set at 0% with PRP and maximal transmission (100%) was set with PPP. The PRP was incubated for 4 min at 37 °C, with stirring 900 rounds × min^{-1}, prior to the addition of ADP. The aggregation response was defined as the increase in light transmission recorded. The ADP (Sigma Chemical, St. Louis, Mo., USA), was kept frozen as a stock solution of 1 μM and was diluted at the time of aggregation studies.

The PRP was exposed to ADP at five final cuvette concentrations: 1, 2, 4, 7 and 10 μM. The rate of aggregation (slope, RA) was determined by drawing a tangent to the steepest part of the aggregation curve. The tangent was then extended so that the increase in light transmission, which occurred within 1 min, could be measured and expressed in arbitrary scale units given by the recording. The maximal increase in light transmission was determined as the recorded increase after 3 min, expressed in percent of maximal light transmission (T-max).

Thrombelastography

Thrombelastography (TEG; Haemoscope, Skokie, Ill., USA) was performed for blood coagulability in whole uncitrated blood (360 μl), using disposable plastic cuvettes and pistons. Whole blood was instilled into the cuvette where the pin was lowered, and a thin layer of liquid paraffin was placed on top of the blood sample. The TEG tracing was measured for reaction time, R (min); clot formation time, K (min); speed of clot formation and fibrin cross-linking, α (°); and maximum clot strength, MA (mm) [26].

Analyses of 6-keto-$PGF_1\alpha$

The metabolite of PGI_2, 6-keto-$PGF_1\alpha$, was analyzed in arterial blood with enzyme immunoassay technique (Cayman Chemical, Ann Arbor, Mich., USA). Blood samples were collected in standard EDTA tubes pretreated with indomethacin dissolved in absolute ethanol, in order to obtain an indomethacin sample concentration of 10 μM to prevent further PGI_2 generation. Samples were centrifuged at a temperature of 5 °C for 15 min at 2000 *g*, and plasma was then immediately removed and frozen (–80 °C) for later analyses.

Table 1 Demographic Data

	Control	PGI_2 5 μg × ml^{-1}	PGI_2 10 μg × ml^{-1}
Age (yr)	67 ± 8	68 ± 7	67 ± 6
Gender (M/F)	6/2	9/1	9/1
Surgery (CABG/AVR)	6/2	8/2	10/0
CPB time (min)	70 ± 7	67 ± 5	60 ± 6
Cross-clamp time (min)	47 ± 6	45 ± 6	35 ± 5
Body surface area (m^2)	1.9 ± 0.06	2.0 ± 0.06	2.0 ± 0.04

CABG = coronary artery by pass grafting, AVR = aortic valve replacement, CPB = cardiopulmonary bypass

Administration of NaCl/PGI_2 aerosol

A jet nebulizer (Engström nebulizing system, ENS; Gambro Engström, Bromma, Sweden) was placed on the inspiratory limb of the ventilator circuit just before the Y-piece, the actual nebulizer chamber separated from the attachment site by a spacer. Nebulizing was triggered to the inspiratory phase of ventilation with a timing device. The volume output from this nebulizer is 0.5 ml × min^{-1} at 2.5 bar. Mean mass diameter (MMD) of generated particles from aqueous solutions is 3.7 μm, according to the manufacturer. PGI_2 was prepared immediately before use, diluted in a glycine buffer (0.188% glycine, 0.147% sodium chloride, pH 10.5) to a concentration of 10 μg × ml^{-1}, and diluted further with sodium chloride to a concentration of 5 μg × ml^{-1}.

Statistical analysis

Data are presented as mean ± SEM. Data were compared using one-way and two-way analysis of variance (ANOVA) for repeated measurements followed by means comparison contrast analysis for evaluation of the differential effects of the different concentrations of PGI_2 [27]. A P value < 0.05 was considered to indicate statistical significance.

Results

Demographic data for the control group and the two PGI_2 groups are given in Table 1. There were no significant differences in age, body surface area, CPB and aortic cross-clamp time or in preoperative hematologic variables. (Table 2) No abnormal bleeding was observed in any patients after cardiac surgery in this study, and there were no differences in total chest tube drainage during inhalation between the groups (control, 170 ± 55 ml; PGI_2 5 μg × ml^{-1}, 192 ± 75 ml; PGI_2 10 μg × ml^{-1}, 176 ± 49 ml). All patients received postoperative autotransfusion. The control group received 214 ± 67 ml (mean ± SEM), the PGI_2 5 μg × ml^{-1}-group, 232 ± 57 ml and the PGI_2 10 μg × ml^{-1}-group, 265 ± 71 ml. There were no differences in volumes received between the different groups.

Table 2 Changes in Hematologic Variables in the Control group and the PGI_2 Groups

	Preop	0 h	2 h	4 h	6 h
Control group (n = 8)					
Hematocrit (%)		39.8 ± 1.2	40.4 ± 0.9	39.4 ± 1.7	39.0 ± 2.1
TPK ($10^9 \times l^{-1}$)	235 ± 19	148 ± 8	167 ± 8	160 ± 7	150 ± 11
PTK (%)	88.2 ± 7.9	64.5 ± 5.5	66.8 ± 4.9	64.7 ± 4.0	63.0 ± 3.6
APTT (s)	33.0 ± 0.9	34.4 ± 1.4	32.8 ± 0.7	37 ± 1.1	37.6 ± 1.1
TEG					
R (min)		9.9 ± 1.2	9.0 ± 1.2	15.1 ± 2.6	15.5 ± 2.1
K (min)		4.4 ± 1.0	4.2 ± 0.6	9.3 ± 2.8	8.6 ± 1.4
α (°)		46.9 ± 6.9	49.0 ± 4.9	27.3 ± 4.1	27.2 ± 3.4
MA (mm)		58.9 ± 3.9	59.2 ± 2.4	62.7 ± 6.7	61.3 ± 5.6
Bleeding time (s)		356 ± 21	322 ± 30	306 ± 24	354 ± 40
PGI_2, 5 μg × ml^{-1} (n = 10)					
Hematocrit (%)		41.6 ± 1.7	41.5 ± 1.7	41.5 ± 2.1	41.0 ± 1.9
TPK ($10^9 \times l^{-1}$)	235 ± 14	172 ± 12	187 ± 12	177 ± 19	179 ± 17
PTK (%)	96.4 ± 8.3	69.7 ± 6.5	69.0 ± 9.0	72.5 ± 9.1	74.5 ± 8.5
APTT (s)	31.8 ± 1.4	30.6 ± 1.2	30.4 ± 1.0	37.8 ± 3.2	34.0 ± 1.6
TEG					
R (min)		14.6 ± 1.2	13.9 ± 3.2	18.7 ± 3.1	15.4 ± 2.0
K (min)		5.7 ± 1.3	9.1 ± 2.0	12.7 ± 2.4	8.7 ± 0.9
α (°)		38.7 ± 4.8	34.5 ± 8.8	24.1 ± 5.2	29.8 ± 5.2
MA (mm)		57.6 ± 2.9	58.5 ± 8.0	53.9 ± 4.1	53.8 ± 4.1
Bleeding time (s)		377 ± 34	340 ± 45	387 ± 84	409 ± 74
PGI_2, 10 μg × ml^{-1} (n =10)					
Hematocrit (%)		41.3 ± 2.6	41.9 ± 1.9	40.8 ± 2.2	38.8 ± 2.0
TPK ($10^9 \times l^{-1}$)	231 ± 16	171 ± 15	187 ± 14	179 ± 15	176 ± 15
PTK (%)	94.3 ± 8.9	64.8 ± 7.4	70.8 ± 7.8	70.8 ± 7.6	69.8 ± 6.4
APTT (s)	33.7 ± 0.6	32.8 ± 0.8	34.2 ± 2.0	39.6 ± 4.7	37.2 ± 1.6
TEG					
R (min)		13.4 ± 3.2	11.2 ± 2.1	32.8 ± 5.1*	27.4 ± 9.8*
K (min)		3.9 ± 0.9	3.4 ± 0.4	13.7 ± 1.5	10.6 ± 2.7
α (°)		40.1 ± 9.9	48.5 ± 4.3	16.0 ± 2.7	23.7 ± 7.8
MA (mm)		51.3 ± 8.6	65.6 ± 7.9	48.4 ± 4.4	55.7 ± 4.2
Bleeding time (s)		354 ± 39	297 ± 24	383 ± 76	325 ± 41

* $p < 0.05$ controlgroup vs PGI_2, 5 μg × ml^{-1} vs PGI_2, 10 μg × ml^{-1}
TPK = platelet count; PTK = prothrombin complex; APTT = activated partial thromboplastin time; TEG = trombelastography; R = reaction time; K = clot formation time; α = speed of clot formation and fibrin cross-linking; MA = maximum clot strength

Hematologic variables and bleeding time

There were no significant differences in hematocrit, platelet count, prothrombin complex, activated partial thromboplastin time or bleeding time between the control group and the two PGI_2 groups (5 μg or 10 μg × ml^{-1}) (Table 2). Skin temperature when determining bleeding time was for all groups within the normal range (36.5–37 °C).

Platelet aggregation

Results of platelet aggregation studies are presented in Fig. 1. Platelet count on all PRP preparations was in the range of 138–211 × $10^9 \times l^{-1}$. The rate of aggregation (RA) and the maximal increase in light transmission (T-max) increased significantly over time in the control group ($P < 0.04$ and $P < 0.006$ respectively). RA was significantly lower after 6 h of inhalation in the two PGI_2groups than in the control group. There was no difference in RA between the groups receiving different concentrations of PGI_2. T-max differed among the groups: significantly lower T-max values were seen in the PGI_2groups than in the control group after 2, 4 and 6 h of inhalation. T-max was also significantly lower in the group who inhaled PGI_2, 10 μg × ml^{-1} than in the PGI_2, 5 μg × ml^{-1}-group after 2 and 4 h of inhalation, while there was no difference between the two PGI_2 groups after 6 h of inhalation. (Fig. 1)

Thrombelastography

Reaction time (R) was significantly greater after 4 and 6 h of inhalation in the group who received PGI_2, 10 μg × ml^{-1} than in the control group and the PGI_2,

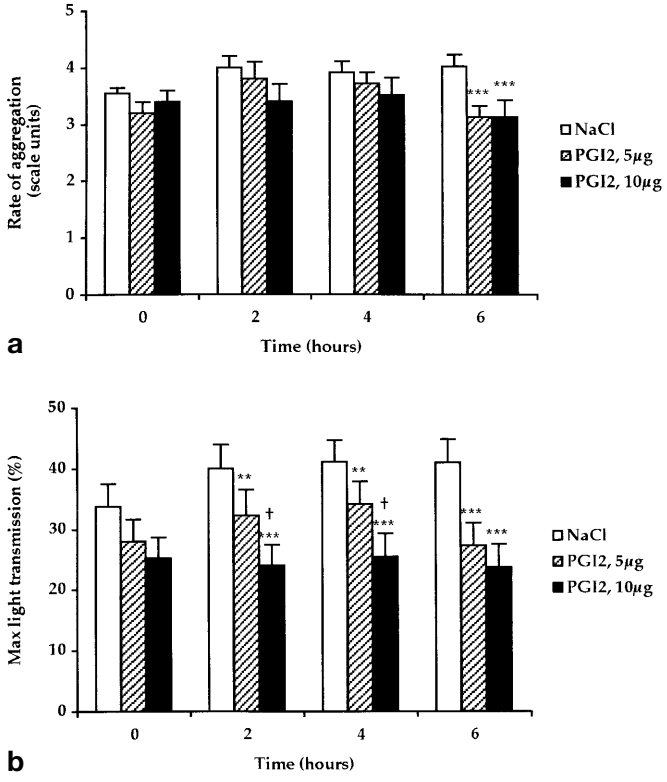

Fig. 1 Mean values of **A** rate of aggregation (RA) and **B** maximal increase in light transmission (T-max) to five fixed cuvette concentrations of adenosine diphosphate after 0, 2, 4 and 6 h inhalation of 0.9% sodium chloride (control) or aerosolized PGI_2 at a concentration of 5 or 10 μg × ml^{-1} after cardiac surgery. *$P < 0.05$, control vs PGI_2, 5 μg × ml^{-1}, control vs PGI_2, 10 μg × ml^{-1}; **$P < 0.01$, control vs PGI_2, 5 μg × ml^{-1}, control vs PGI_2, 10 μg × ml^{-1}; ***$P < 0.001$, control vs PGI_2, 5 μg × ml^{-1}, control vs PGI_2, 10 μg × ml^{-1}; $^{\dagger}P < 0.05$, PGI_2, 5 μg × ml^{-1} vs PGI_2, 10 μg × ml^{-1}

5 μg × ml^{-1} group (Table 2). No other differences in TEG variables were found among the different groups.

6-keto-$PGF_1\alpha$

There were no differences in plasma concentrations of 6-keto-$PGF_1\alpha$ between the control group and the two PGI_2 groups (Fig. 2).

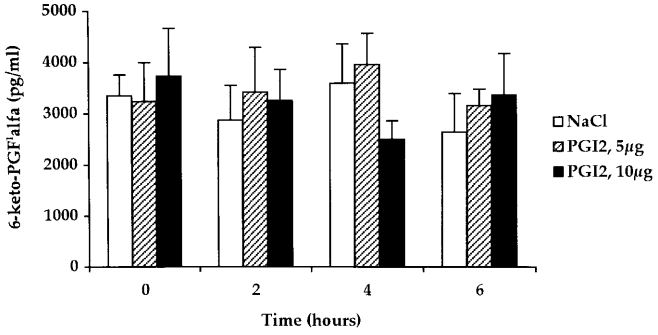

Fig. 2 Mean values of the stable metabolite of PGI_2, 6-keto-$PGF_1\alpha$, after 0, 2, 4 and 6 h inhalation of 0.9% sodium chloride (control) or aerosolized PGI_2 at a concentration of 5 or 10 μg × ml^{-1} after cardiac surgery

Discussion

The present study indicates that inhalation of aerosolized PGI_2 for 6 h postoperatively in cardiac surgical patients causes significant dose- and time-dependent changes in the in vitro platelet aggregation response. The physiological recovery of platelet function in vitro after cardiopulmonary bypass was thus attenuated by PGI_2 inhalation. However, no changes in in vivo estimates of platelet function were detected, i.e. no differences in bleeding time and chest tube drainage were seen among the groups.

Besides its vasodilatory properties, PGI_2 is the most potent endogenous inhibitor of platelet activation yet discovered, even dispersing aggregated platelets [22, 28]. Therefore, effects on platelet function by inhaled PGI_2 (see below) must be considered, especially in cardiac surgical patients already suffering from hemostatic perturbation caused by CPB [29, 30].

The mechanism behind the anti-aggregatory effect of inhaled PGI_2 could be caused by a direct binding of PGI_2 to specific receptors when platelets pass the pulmonary circulation. Inhaled PGI_2 may diffuse into the different layers of the vessel wall, resulting in vasodilation and uptake of PGI_2 into platelets exposed to the endothelium. It may also be caused by a "spill-over" of PGI_2 into the systemic circulation with increased plasma concentrations of PGI_2 and consequent inhibition of platelet activation. In previous reports on the effects of inhaled PGI_2 on patients with ARDS it has been suggested that such a "spill-over" might occur in individual patients [31]. This mechanism is less likely to explain the anti-aggregatory effects of inhaled PGI_2 as demonstrated in the present study, since there were no differences among groups in plasma levels of the non-enzymatically formed stable PGI_2 metabolite 6-keto-$PGF_1\alpha$ and measured values were in the range of previously recorded levels after CPB [32]. We have previously shown that inhalation of PGI_2 by patients with pulmonary hypertension using the same concentrations as in the present study did not induce systemic vasodilation, which is indirect evidence that inhaled PGI_2, in these concentrations, does not "spill over" to the systemic circulation [11, 33]. Furthermore, in an experimental animal setting, inhalation of PGI_2 28 ng × kg × min^{-1} for 8 h did not result in systemic effects or increased levels of 6-keto-$PGF_1\alpha$.

Evidence that inhaled aerosolized PGI_2 may induce selective pulmonary vasodilation was first provided by Welte et al. in a canine model of pulmonary hypertension [34]. The intratracheal route of delivery of PGI_2 has since attracted increasing interest in the treatment of pulmonary hypertension of various origins and for evaluation of heart transplant candidates with elevated PVR [11, 13, 14, 15, 16, 17, 19, 33]. The obvious advantage of its administration, using standard and generally available nebulizing systems, makes inhaled PGI_2 an attractive therapeutic option. Persistent elevated PVR and right ventricular failure after cardiac surgery or heart transplantation may prolong the need for vasodilatory therapy, with accompanying potential negative effects on platelet function.

The amount of inhaled PGI_2 reaching the alveolar space cannot be precisely measured because of losses in the nebulizer chamber, ventilator tubing and the endotracheal tube. Furthermore, alveolar deposition of aerosol during mechanical ventilation has been estimated at less then 10 %. These uncertainties regarding the dosing are a concern [35]. A dose-response procedure as performed in an earlier study by our group is a familiar and safe procedure in well-monitored cardiac surgical patients. We therefore chose two different doses, used in this earlier design, known to reduce PVR without systemic effects [11]. The pulmonary deposition of PGI_2 was not assessed in this study but mean doses delivered by the nebulizer was 30 and 62 ng $\times$ kg^{-1} $\times$ min^{-1}, which correspond to a medium and a high dose relative to doses previously reported in man (2–50 ng $\times$ kg^{-1} $\times$ min^{-1}) by other authors [13, 14, 15, 16, 17, 19, 20, 21, 22].

In our study, impaired platelet aggregation response to ADP, beyond the acquired platelet dysfunction due to CPB, was evident after 2 h of inhalation regardless of the dose of aerosolized PGI_2 administered. This test provides a sensitive modality for evaluating platelet function in vitro [25]. However, the role of platelets for hemostasis in vivo is far more complicated. Therefore, platelet function measured in vitro does not necessarily reflect platelet function in vivo, as demonstrated by the lack of effects of inhaled PGI_2 on bleeding time or chest tube drainage compared to control. Consistent with prevailing CPB-induced hemostatic changes, platelet count decreased significantly in all groups from preoperative recorded values, with no differences between the groups. In other words, the anti-aggregatory effects of PGI_2 in this study could not be explained by differences in platelet count.

The in vitro TEG variable reaction time (R) increased significantly after 4 and 6 h of inhalation in the group receiving PGI_2, 10 μg $\times$ ml^{-1}, compared with control. This may be related to the diminished platelet reactivity induced by PGI_2, thereby affecting the intrinsic activation of coagulation. Importantly, the final outcome, clot strength (MA), remained unaffected for all groups during inhalation. The MA is influenced by both platelet number and function and also by fibrinogen and thrombin concentration, fibrin, factor XIII and hematocrit [26]. It has also been reported to be a sensitive variable for detection of postoperative abnormal coagulation [36]. However, global reading of the TEG variables is considered to provide better information than that derived from the analysis of an isolated parameter [26].

A limitation of this study is that we included patients undergoing uncomplicated routine surgery, and that the duration of administration of PGI_2 was only 6 h. The results do not increase our knowledge on the effects of long-term inhalation of aerosolized PGI_2 in patients with pulmonary hypertension after a more complicated surgical procedure requiring longer CPB time. Also, for logistic reasons, it was not possible to perform follow-up measurements of all the presented variables after termination of inhalation. Any rebound occurrences thus escaped detection. All patients were sedated with propofol during the experimental procedure, which might be of concern as there is some [37], albeit conflicting [38], information that propofol might suppress platelet aggregation. The combined effects of PGI_2 and propofol on platelet aggregation has previously not been studied.

In summary, we conclude that 6 h inhalation of aerosolized PGI_2 in a medium and a high dose after cardiac surgery reduced ADP-induced platelet aggregation in vitro, regardless of dose administered. The clinical significance of these findings is not immediately evident, as there were no in vivo signs of platelet dysfunction such as increases in bleeding time or chest tube drainage.

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