REPORTS OF ORIGINAL INVESTIGATIONS

Effect of iloprost inhalation on postoperative outcome in high-risk cardiac surgical patients: a prospective randomized-controlled multicentre trial (ILOCARD)

Effet de l'inhalation d'iloprost sur le pronostic postopératoire chez les patients chirurgicaux cardiaques à haut risque : une étude multicentrique randomisée et prospective (ILOCARD)

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Abstract

Purpose *Perioperative right ventricular (RV) failure due to pressure overload from pulmonary hypertension (PH) worsens postoperative outcomes after cardiac surgery. Inhaled iloprost is a potent pulmonary vasodilator improving RV performance, ameliorating myocardial and pulmonary ischemia-reperfusion injury and attenuating*

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inflammation. We hypothesized that the prophylactic inhalation of iloprost would reduce postoperative ventilation times after cardiac surgery.

Methods *In this phase III, multicentre, randomized, double-blind, placebo-controlled trial, we randomly assigned 253 cardiac surgical patients at high risk of perioperative RV failure to the prophylactic inhalation of 20 µg iloprost or placebo before and during weaning from extracorporeal circulation. The primary endpoint was the duration of postoperative ventilation. Secondary endpoints included perioperative hemodynamics, intensive care unit and hospital length of stay, and 90-day mortality. Safety was assessed by the incidence of adverse events.*

Results *Iloprost had no significant effect on the median [interquartile range] duration of postoperative ventilation compared with placebo (720 [470–1170] min vs 778 [541–1219] min, respectively; median decrease, 65 min; 95% confidence interval [CI], − 77 to 210; P = 0.37). While the*

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nebulization of iloprost decreased RV afterload and improved cardiac index, major secondary endpoints were not significantly affected. Ninety-day mortality occurred in 14% of the iloprost patients compared with 14% of the placebo patients (hazard ratio, 0.97; 95% CI, 0.50 to 1.89; P = 0.93). The incidence of adverse events was comparable in both groups.

Conclusions The prophylactic inhalation of iloprost did not meaningfully improve the outcome in high-risk cardiac surgical patients.

Trial registration www.clinicaltrials.gov (NCT00927654); registered 25 June, 2009.

Résumé

Objectif L'insuffisance cardiaque droite périopératoire due à une surcharge de pression provoquée par l'hypertension pulmonaire (HP) a un impact négatif sur le pronostic postopératoire après une chirurgie cardiaque. L'iloprost administré par inhalation est un vasodilatateur pulmonaire puissant qui améliore la performance du ventricule droit (VD), réduisant ainsi la lésion d'ischémie-reperfusion myocardique et pulmonaire et atténuant l'inflammation. Nous avons émis l'hypothèse qu'une inhalation prophylactique d'iloprost réduirait les temps de ventilation postopératoire après une chirurgie cardiaque.

Méthode Dans cette étude multicentrique de phase III, contrôlée par placebo, à double insu et randomisée, nous

avons distribué aléatoirement 253 patients chirurgicaux courant un risque élevé d'insuffisance cardiaque droite périopératoire à une prophylaxie de 20 µg d'iloprost ou d'un placebo par inhalation avant et pendant le sevrage de la circulation extracorporelle. Le critère d'évaluation principal était la durée de ventilation postopératoire. Les critères d'évaluation secondaires étaient les données hémodynamiques périopératoires, la durée de séjour à l'unité de soins intensifs et à l'hôpital, et la mortalité à 90 jours. L'innocuité a été évaluée en fonction de l'incidence d'événements indésirables.

Résultats L'iloprost n'a pas eu d'effet significatif sur la durée médiane [écart interquartile] de ventilation postopératoire par rapport au placebo (720 [470–1170] min vs 778 [541–1219] min, respectivement; réduction médiane, 65 min; intervalle de confiance [IC] 95 %, − 77 à 210; P = 0,37). Bien que la nébulisation d'iloprost ait réduit la post-charge du VD et amélioré l'index cardiaque, cette manœuvre n'a pas eu d'impact significatif sur les critères d'évaluation secondaires majeurs. Une mortalité à 90 jours a été observée chez 14 % des patients ayant reçu de l'iloprost, comparativement à 14 % des patients ayant reçu un placebo (rapport de risque, 0,97; IC 95 %, 0,50 à 1,89; P = 0,93). L'incidence d'événements indésirables était comparable dans les deux groupes.

Conclusion L'inhalation prophylactique d'iloprost n'a pas amélioré le pronostic des patients de chirurgie cardiaque à haut risque.

Enregistrement de l'étude www.clinicaltrials.gov (NCT00927654); enregistrée le 25 juin 2009.

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Cardiac surgery with the use of extracorporeal circulation (ECC) elicits a systemic inflammatory response that is triggered by contact of blood with non-endothelial surfaces, cardiopulmonary ischemia-reperfusion injury, endotoxemia, and surgical trauma.[2] Systemic inflammation is associated with pulmonary artery (PA) endothelial dysfunction.[3] After termination of ECC, an increased release of vasoconstrictory endothelin and a decreased production of vasodilatory nitric oxide (NO) was found to be correlated with significant increases in pulmonary vascular tone.[4,5] Perioperative increases in pulmonary vascular resistance result in acute new-onset or acute-on-chronic pulmonary hypertension (PH), which are usually not well tolerated by the right ventricle. If the increase in right ventricular (RV) afterload continues or is aggravated, the right ventricle will eventually fail and initiate a self-aggravating cascade of circulatory shock. In fact, RV dysfunction has been repeatedly shown to dramatically worsen the outcome after cardiac surgery.[6–8]

One strategy for the therapy of perioperative RV dysfunction is to lower RV afterload with intravenously administered vasodilators, which lack pulmonary selectivity[9] and may perpetuate a vicious cycle of hypotension, leftward septal shift, RV ischemia, and shock.[10] In contrast, selective pulmonary vasodilation can be achieved by inhalation of vasodilators.[11] While this strategy was proven to improve systemic and pulmonary hemodynamics, beneficial effects on "harder" outcome parameters have not been shown yet, partly due to the lack of adequately powered studies with morbidity and/or mortality as the primary outcome.[12]

Because it is easy to administer and is not toxic, intermittent nebulization of iloprost has become increasingly popular in the treatment of postcardiotomy RV dysfunction.[9,13,14] Iloprost, the stable carbacyclin derivative of prostacyclin (PGI_2), is a potent pulmonary vasodilator that lowers RV afterload at least as effectively as inhaled NO.[15] Moreover, iloprost and PGI_2 improved biventricular performance,[16-18] exerted anti-inflammatory effects,[19] ameliorated myocardial ischemia-reperfusion injury,[20] improved oxygenation in adult respiratory distress syndrome,[21] attenuated pulmonary ischemia-reperfusion injury,[22] improved the pulmonary clearance of endothelin,[23] and reduced oxidative stress and counteracted platelet activation with consecutive microthrombosis.[24]

On the background of these beneficial effects, we hypothesized that the prophylactic inhalation of iloprost would improve perioperative morbidity and outcome in patients undergoing elective heart surgery with ECC and at an increased risk for perioperative RV failure. The primary outcome parameter considered was the duration of postoperative ventilation, which we considered as a surrogate parameter for the severity of critical illness in cardiac surgical patients and is prolonged by PH, RV failure, shock, and prolonged ECC times.[25–27]

Methods

Trial design and population

The "Effect of ILOprost inhalation before and during EEC on perioperative morbidity and outcome in high-risk CARDiac surgical patients" (ILOCARD) study was a prospective, multicentre, randomized, double-blind, placebo-controlled, phase III trial, conducted in six German heart centres. It was approved by the local ethics committee of each participating institution (leading ethics committee: ethics committee of the Medical Faculty of the LMU München, project number 419-08, January 28, 2009) and by Germany's Federal Institute for Drugs and Medical Devices (BfArM, 4034768, March 4, 2009). The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT00927654, Principal investigator: B. Zwissler, Date of registration: June 25, 2009) and at the EU clinical trials register (EudraCT 2008-002090-12, Date: March 4, 2009). Note that iloprost is not labelled for clinical use under investigation in this trial.

Written informed consent was obtained from all patients. We enrolled patients ≥ 18 and ≤ 85 yr of age scheduled for elective open-heart surgery with the assistance of ECC and with an increased risk of perioperative RV failure. The latter was assumed by 1) the necessity to undergo complex cardiac surgery (surgery on ≥ 2 valves or expected duration of ECC > 120 min), or 2) the presence of preoperative PH (mean pulmonary arterial pressure [mPAP] > 30 mmHg measured by RV catheterization or a systolic PAP ≥ 60 mmHg measured by echocardiography at screening), or 3) the presence of congestive heart failure (New York Heart Association [NYHA] class $\geq$ III).[6] Patients were excluded if they had known hypersensitivity to iloprost or other prostaglandins, were pregnant or breastfeeding, suffered from primary or secondary immune deficiency or an acute systemic infection, had lung disease with impaired gas exchange (partial pressure of oxygen [PaO_2] < 60 mmHg at the fraction of inspired oxygen [F_IO_2] of 0.21 mmHg), had a hemorrhagic diathesis, thrombocytopenia < 50,000 /μl or other coagulation disorders, suffered from recent trauma, current ulcer, intracerebral hemorrhage or stroke (< three months ago), or were scheduled for lung transplantation, heart transplantation, left ventricular assist device implantation or for deep hypothermic cardiocirculatory arrest. Female patients of childbearing potential were required to use a reliable method of contraception.

Randomization/allocation and concealment/blinding

Patients were randomized using a computer-generated permuted block randomization sequence (block size 6, 1:1 allocation). Randomization was stratified by centre and by dichotomizing the major prognostic score of the European System for Cardiac Operative Risk Evaluation (EuroSCORE) using a cutoff of 10 (Stratum I: EuroSCORE ≤ 10; Stratum II: EuroSCORE > 10). Study drugs were sealed in sequentially numbered identical containers that were provided to the participating centres in balanced blocks according to the allocation sequence. The study medication was prepared by an independent operator not otherwise involved in the trial (Pharmacy of the Heidelberg University Hospital, Heidelberg, Germany). Iloprost and placebo medication were identical in colour, appearance, shape, and size. All investigators were blinded to treatment allocation throughout the entire study, including the data

management and the trial statistician until the completion of a blinded data review meeting.

Intervention

Participating patients were 1:1 randomized to the inhalation of 20 µg iloprost (2 mL Ventavis®, Bayer Vital GmbH, Leverkusen, Germany) or 2 mL placebo (saline 0.9%, B Braun Melsungen AG, Melsungen, Germany) twice, immediately prior to the start of ECC (to test the hypothesis that iloprost would counteract ECC-induced pulmonary inflammation) and after release of the aortic cross-clamp (before weaning from ECC). Study drugs were administered over a time period of five to ten minutes via an electronic micropump nebulizer using vibrating mesh nebulization technology (Aeroneb® Solo, Aerogen Ltd., Galway, Ireland). This nebulizer delivers particles with a mass median aerodynamic diameter of 3.4 µm.

Perioperative management

Intraoperative anesthesia, perioperative hemodynamic treatment, coagulation therapy, and intensive care unit (ICU) management were performed according to the institutional standards of the participating centres. The patients received standard cardiorespiratory monitoring plus pulmonary arterial catheterization.

Prior to and after ECC, all patients were ventilated using pressure-controlled ventilation and maintaining normocapnia. Before weaning from ECC and the second study drug inhalation, a manual recruitment maneuver was performed with subsequent adjustment of positive end-expiratory pressure (PEEP). During weaning from EEC, patients were ventilated with 100% oxygen.

After completion of surgery, patients were transferred to the ICU.

Extubation protocol in the ICU

After admission to the ICU, patients were sedated with a continuous infusion of propofol ($3–5$ mg·kg^{-1}·hr^{-1}) and a pre-defined extubation protocol was applied. Sedation was stopped once the patient was hemodynamically stable, normothermic (core temperature $> 36°C$) and pulmonary gas exchange was sufficient ($F_iO_2 < 50\%$, PEEP < 10 cmH$_2$O, PaO$_2 > 90$ mmHg). Patients were considered to be suitable for extubation once they were awake and responsive to verbal stimuli, were hemodynamically stable, had no significant blood loss (< 100 mL·hr^{-1} via the chest drains), and accomplished the following ventilatory parameters: $F_iO_2 < 45\%$, PEEP < 10 cmH$_2$O, PaO$_2 > 90$ mmHg, spontaneous respiratory rate > 10/min, and spontaneous respiratory minute volume 75–150 mL·kg^{-1}).

Trial endpoints

Efficacy endpoints

The primary efficacy endpoint was the duration of postoperative ventilation (defined as the time between admission to the ICU and protocol-guided extubation, or as the time between ICU admission and death if the patient died before extubation).

Secondary efficacy endpoints included incidence of failure to wean from ECC (defined as the requirement for multiple weaning attempts with the weaning protocol left at the discretion of the study centre); incidence of RV failure 30 min after termination of ECC and during the first 24 hr postoperatively (diagnosed by the combination of a sudden increase in central venous pressure in excess of PA occlusion pressure, typical echocardiographic criteria [RV end-diastolic area $>$ left ventricular end-diastolic area], and/or direct visual inspection intraoperatively); incidence of PH (mean PAP > 25 mmHg) 30 min after end of ECC and six hours postoperatively; incidence of acute hypoxemic respiratory failure (PaO$_2$/F$_i$O$_2 < 300$ mmHg) 30 min after end of ECC and six hours postoperatively; systemic and pulmonary hemodynamics after induction of anesthesia, 30 min after end of ECC, one hour and six to 12 hr after admission to the ICU; requirement to use vasopressors, inotropes, and other rescue medication six hours postoperatively (left at the discretion of the attending investigator); perioperative systemic inflammation (plasma levels of interleukin [IL]-6 and tumour necrosis factor [TNF]-α obtained after induction of anesthesia and six to 12 hr after ICU admission); postoperative pulmonary inflammation (levels of IL-6 and TNF-α determined from bronchoalveolar lavage [BAL] fluid six to 12 hr after ICU admission, using enzyme-linked immunosorbent assays); ICU and hospital length of stay; and 90-day mortality.

Exploratory endpoints

Arterial serum levels of iloprost were also measured (for analytical details, see electronic supplemental material [ESM]).

Safety endpoints

Safety endpoints measured included the incidence of re-thoracotomy for bleeding, incidence of intracranial

hemorrhage, stroke, and pneumonia, and the incidence of other (serious) adverse events.

Sample size estimation

Sample size determination was based on testing the primary endpoint for differences at a two-sided type I error level of 5% (2.5% each for superiority and inferiority) using the non-parametric Wilcoxon-Mann-Whitney test. According to the experience of the participating centres and following the published literature,[28,29] we expected a mean time of 24 hr postoperative ventilation in survivors from the high-risk study population. Assuming a standard deviation of 16 hr and a mortality of 10%, we calculated that in case of equal group size, 124 patients per group were needed to detect a seven-hour reduction in the time of postoperative ventilation with a power of 80%. Coping with slight imbalances of the group sizes at random, we aimed to randomize until at least 250 patients could be included in the statistical analysis.

Statistical analysis

Analyses were performed with SAS, versions 9.3 and 9.4 (SAS Institute, Cary, NC, USA), StatXact of Cytel Studio, version 6.3.0 (Cytel Studio; Cytel Corporation, Cambridge, MA, USA), and the R Project for Statistical Computing. All analyses were conducted primarily on an intention to treat (ITT) basis. The primary endpoint was compared between the two groups using the Wilcoxon-Mann-Whitney test. Thereby, patients dying before extubation were assessed with worst ranks, using the hierarchical order "worse when dying during surgery than after admission to ICU" in general, and "worse when dying early" for the two time periods in which death could occur (intraoperatively *vs* during ICU stay). The pre-defined primary test adjusts for risk strata I and II, i.e., for EuroSCORE $\leq/>$ 10. Confidence intervals (CIs) for the location shift were calculated using the method of Hodges and Lehmann. Moreover, to verify the robustness of the result, sensitivity analyses were performed using per protocol sets, using a linear regression model with the rank as dependent variable (adjusting for age, sex, and EuroSCORE), and by modelling competing risks with an analysis of cause-specific hazards (adjusted for the identical factors). In addition, the treatment effect was calculated separately for both risk strata. For the analysis of the secondary endpoints and the exploratory analyses, continuous variables were tested using the Wilcoxon-Mann-Whitney test. Categorical variables were compared using the Fisher's exact test. Time-to-event outcomes were described with the Kaplan-Meier technique, and the treatment effect was compared between the two groups using a log-rank test. The treatment effect is reported in hazard ratios (HR) that were derived from a Cox regression. All endpoints were analyzed both unstratified (unadjusted) and stratified (adjusted) for the EuroSCORE $\leq$ or $>$ 10.

All endpoints and statistical methodology were defined before unblinding, except for the post hoc exploratory subgroup analyses and analyses of the hemodynamic parameters. For the latter, we performed an explanatory intergroup comparison six to 12 hr after admission to the ICU (T5). In addition, hemodynamic parameters were modelled over time assuming that the parameters are normally distributed. Results of linear mixed models with treatment and time (factor with repeated measurements at T2, T3, T4, and T5, i.e., just prior to and 30 min after end of ECC, one hour and six to 12 hr after admission to the ICU, respectively) as fixed effects and the baseline parameter value after induction of anesthesia (T1) as covariable were provided.

All reported *P* values are two-sided.

Results

Patients

From June 16, 2009 to December 12, 2011, 253 patients were enrolled. Of these patients, 122 were randomized to receive placebo, and 131 were assigned to receive iloprost (Fig. 1). One patient in the iloprost group withdrew informed consent for surgery after enrollment into the study, thus underwent neither surgery nor anesthesia and could not be evaluated for the primary endpoint. Therefore, the ITT population consisted of 252 patients. Baseline characteristics of the patients are depicted in Table 1.

Primary efficacy endpoint

Groups did not differ significantly with respect to median [interquartile range (IQR)] duration of postoperative ventilation (720 [470–1170] min iloprost *vs* 778 [541–1219] min placebo; median decrease [Hodges-Lehmann], 65 min; 95% CI, − 77 to 210 min; unadjusted *P* = 0.37) (Fig. 2, Table 2). In a pre-planned post hoc analysis and according to the prognostic relevance, the primary analysis was adjusted for the EuroSCORE by stratification (increase EuroSCORE stratum II *vs* stratum I, 355 min, *P* < 0.001). Iloprost similarly did not significantly reduce the duration of postoperative ventilation (Hodges-Lehmann decrease) in stratum I by 35 min (95% CI, –115 to 179) or in stratum II by 180 min (95% CI, − 315 to 715).
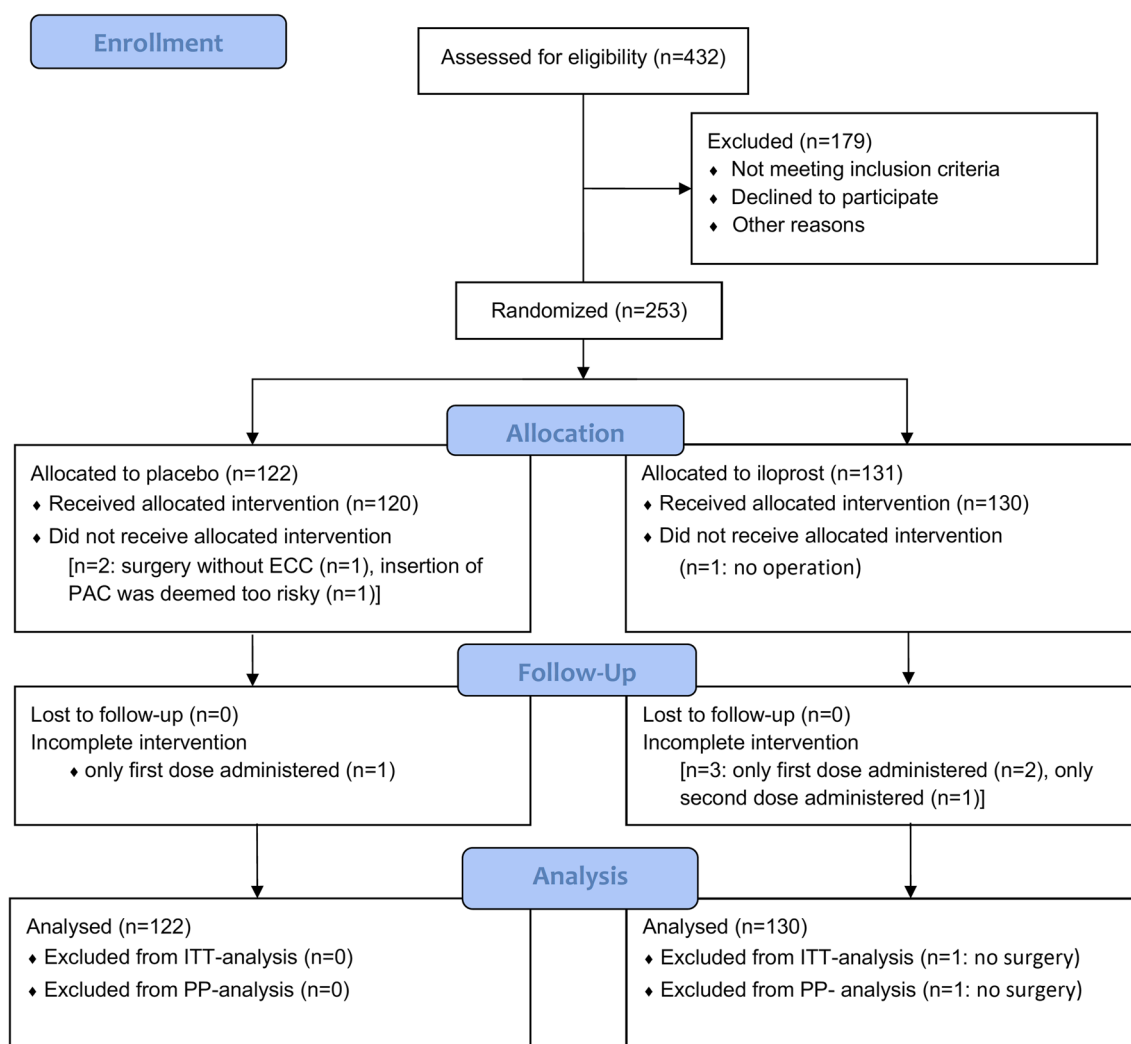
Fig. 1 Flow diagram presenting enrollment, intervention allocation, follow-up and data analysis. ITT = intention to treat; PAC = pulmonary artery catheter; PP = per protocol

Table 1 Clinical characteristics of the patients at baseline

		Placebo (*n* = 122)	Iloprost (*n* = 131)
Age	y	73.3 [67.1–78.0]	72.6 [65.0–76.5]
Sex: male/female	*n* (%)	70/52 (57/43)	73/58 (56/44)
BMI	kg·m^{-2}	26.3 [23.8–29.0]	26.4 [23.6–30.1]
EuroSCORE I		9 [7–11]	9 [7–11]
Stratum I/II	*n* (%)	90/32 (74/26)	97/34 (74/26)
LVEF	%	49 [35–60]	45 [35–60]
NYHA class I/II/III/IV	*n* (%)	8/35/75/4 (7/29/61/3)	8/32/84/5 (6/25/65/4)
Valvular heart disease	*n* (%)	117 (96)	123 (94)
Ischemic heart disease	*n* (%)	80 (66)	80 (62)
Pulmonary hypertension	*n* (%)	75 (62)	72 (55)

Data are presented as median [interquartile range] or as absolute numbers (with the % of the patients within each group)

BMI = body mass index, EuroSCORE = European System for Cardiac Operative Risk Evaluation, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, Stratum I: EuroSCORE ≤ 10, Stratum II: EuroSCORE > 10
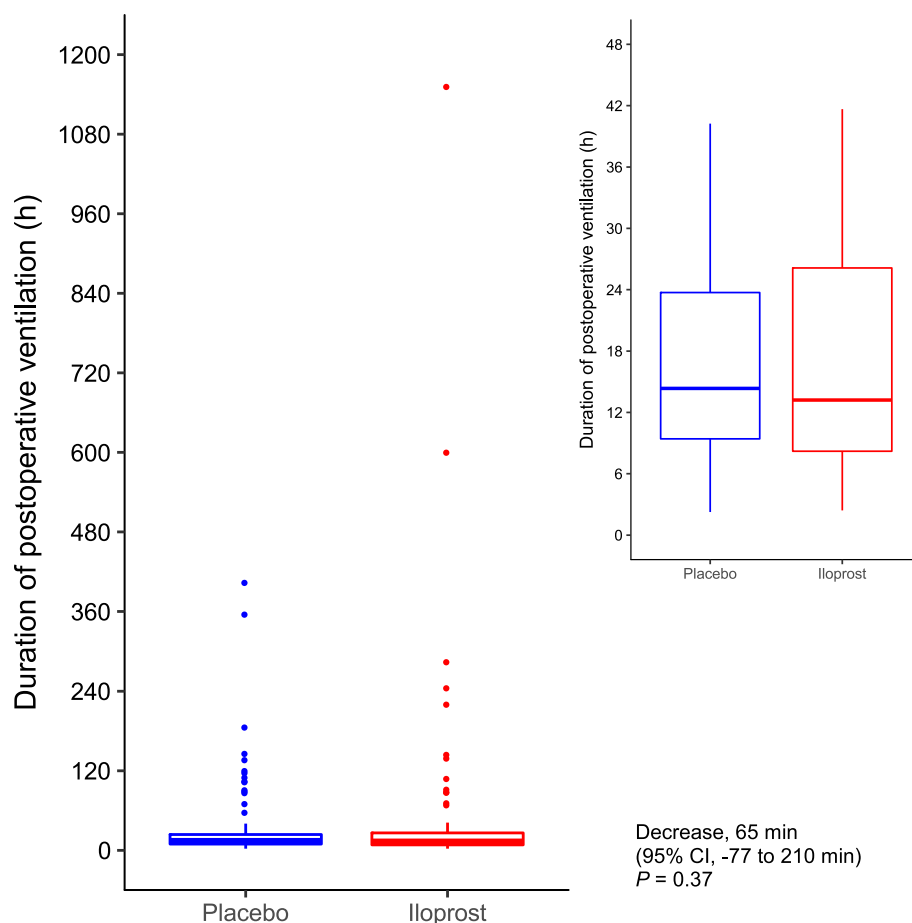
Fig. 2 Comparing the distribution of the primary endpoint "duration of postoperative ventilation" in high-risk cardiac surgical patients receiving inhaled iloprost or placebo twice during cardiac surgery. The distribution was compared between both groups using the Wilcoxon-Mann-Whitney test and the Hodges-Lehmann estimator for the location shift. Adjusting for the EuroSCORE by stratification ($\leq$ or > 10), the exact P-value and estimate of decrease by iloprost with 95% confidence interval are provided. Thereby, patients dying before regular extubation were assessed with worst ranks, using the hierarchical order "worse when dying during surgery than after admission to intensive care unit (ICU)" in general, and "worse when dying early" for the two time periods in which death could occur (intraoperatively *vs* during ICU stay). The lower hinge of the box indicates the 25th percentile, the line within the box marks the median, and the upper hinge of the box indicates the 75th percentile. Whiskers extend from the lower and the upper hinge up to the lowest and the highest value within 1.5 times the interquartile range lower and higher than the hinge, respectively, while closed circles represent outliers. The iloprost group consists of 112 values plus ten worst ranks, the placebo group of 121 values plus nine worst ranks. The inlay shows a magnification of the main figure without displaying the outliers (note that they were still included in the calculation of the percentiles)

Secondary efficacy endpoints

Groups did not differ with respect to the majority of secondary efficacy endpoints (Table 2), neither in the unadjusted nor in the stratified analysis (adjusted results not always shown).

Ninety-day mortality occurred in 18 iloprost patients (14%; 95% CI, 8 to 20) compared with 16 placebo patients (14%; 95% CI, 7 to 20) (unadjusted HR, 0.97; 95% CI, 0.50 to 1.88; $P = 0.92$; HR EuroSCORE stratum II *vs* stratum I, 3.23; $P < 0.001$; adjusted HR, 0.97; 95% CI, 0.50 to 1.89, $P = 0.93$) (Fig. 3).

Failure to wean from ECC occurred in 3 (2.3%) of the patients in the iloprost group *vs* 9 (7.5%) in the placebo group (odds ratio, 0.29; 95% CI, 0.050 to 1.22; $P = 0.08$).

PERIOPERATIVE HEMODYNAMICS

Overall, the inhalation of iloprost significantly increased the cardiac index, and decreased systemic and pulmonary vascular resistance indices. Nevertheless, these differences were not sustained as the separate analysis of the intergroup comparison six hours after admission to the ICU failed to show any significant differences (Table 3).

Table 2 Efficacy outcomes

		Placebo (n = 122)	Iloprost (n = 130)	Difference*/Odds ratio† (95% CI)	P value
Primary endpoint					
Duration of postop. ventilation	hr	13.0 [9.0–20.3]**	12.0 [7.8–19.5]**	1.08 (− 1.28 to 3.50)***	0.37***
Deaths before extubation	n (%)	10 (8.2)	9 (6.9)	0.83 (0.29 to 2.38)	0.81
Secondary endpoints					
ICU length of stay	d	4 [2–7]	4 [2–7]	0 (− 1 to 1)	0.79
Hospital length of stay	d	13 [10–20]	13 [9–19]	1 (− 1 to 3)	0.35
Failure to wean from ECC	n (%)	9 (7.5)	3 (2.3)	0.29 (0.050 to 1.22)	0.08
RVF at end of ECC	n (%)	8 (6.7)	6 (4.7)	0.68 (0.19 to 2.33)	0.40
RVF 24 hr postop.	n (%)	8 (6.8)	7 (5.5)	0.80 (0.24 to 2.61)	0.78
PH after sternal closure	n (%)	70 (63.6)	74 (60.7)	0.88 (0.50 to 1.55)	0.69
PH 6 hr postop.	n (%)	69 (66.3)	81 (71.1)	1.25 (0.67 to 2.30)	0.47
ALI at end of ECC	n (%)	72 (61.5)	71 (56.8)	0.82 (0.48 to 1.42)	0.51
ALI 1 hr postop.	n (%)	61 (51.7)	65 (52.0)	1.01 (0.59 to 1.73)	1.00
ALI 6 hr postop.	n (%)	44 (43.6)	53 (49.1)	1.25 (0.70 to 2.23)	0.49
Use of rescue medication					
Dobutamine	n (%)	65 (53.3)	58 (44.6)	0.71 (0.42 to 1.20)	0.21
Epinephrine	n (%)	58 (47.5)	58 (44.6)	0.89 (0.53 to 1.50)	0.70
Norepinephrine	n (%)	104 (85.2)	116 (89.2)	1.43 (0.64 to 3.28)	0.35
Milrinone	n (%)	46 (37.7)	46 (35.4)	0.90 (0.52 to 1.56)	0.79
iNO	n (%)	6 (4.9)	8 (6.2)	1.27 (0.37 to 4.57)	0.79
Iloprost	n (%)	19 (15.6)	21 (16.2)	1.04 (0.50 to 2.18)	1.00

* Difference (italic letters): placebo minus iloprost †Odds ratio: iloprost vs placebo

** Deaths before extubation not considered *** Deaths before extubation considered as worst ranks. Data are presented as median [first quartile, third quartile] or as absolute numbers (with the percentage (%) of the patients within each group). Continuous variables were tested using the Wilcoxon-Mann-Whitney test. Categorical variables were compared by means of the Fisher's exact test. Confidence intervals were calculated using the method of Hodges and Lehmann. ALI = acute lung injury; ECC = extracorporeal circulation; ICU = intensive care unit; PH = pulmonary hypertension; postop. = postoperative; RVF = right ventricular failure

Fig. 3 Kaplan-Meier estimated postoperative mortality in high-risk cardiac surgical patients receiving inhaled iloprost or placebo twice during cardiac surgery. ECC = extracorporeal circulation
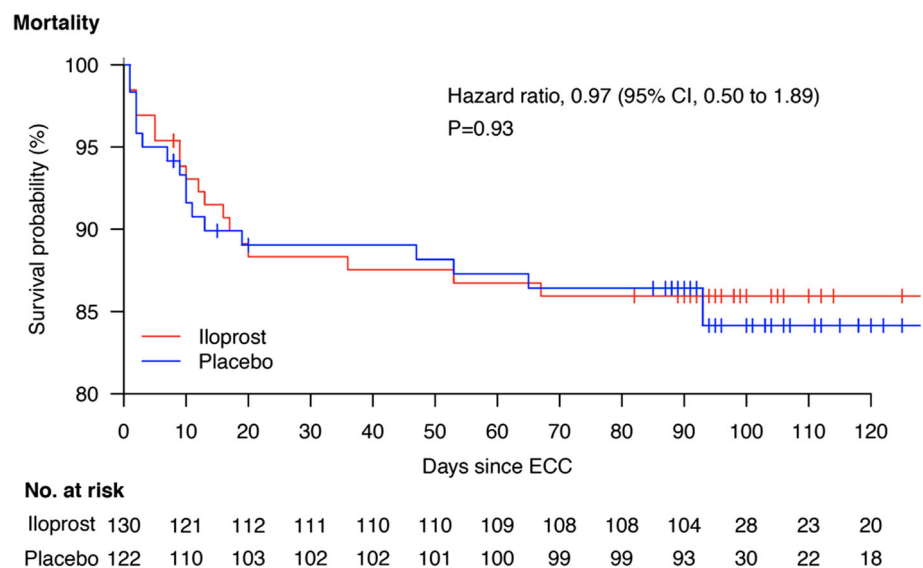
Table 3 Perioperative hemodynamic data

	Treatment	T 1 n	Median [IQR]	T 2 N	Median [IQR]	T 3 n	Median [IQR]	T 4 n	Median [IQR]	T 5 n	Median [IQR]	P_{T5}	Treatment effect (SE)	P
HR (min⁻¹)	Placebo	111	60 [53–69]	118	67 [56–77]	119	91 [89–97]	119	92 [89–97]	117	90 [89–97]	0.63	0.50 (1.09)	0.65
	Iloprost	120	63 [55–75]	125	69 [60–80]	127	92 [89–99]	125	91 [89–99]	123	90 [86–97]			
MAP (mmHg)	Placebo	111	73 [63–83]	118	74 [64–85]	118	73 [64–80]	118	74 [66–85]	117	76 [67–84]	0.57	− 1.19 (0.97)	0.22
	Iloprost	118	76 [67–85]	125	71 [62–80]	127	69 [63–78]	125	75 [68–83]	122	75 [66–82]			
CVP (mmHg)	Placebo	110	13 [9–17]	116	11 [8–15]	119	14 [10–17]	119	13 [10–17]	116	12 [11–15]	0.66	− 0.45 (0.37)	0.22
	Iloprost	116	13 [10–17]	124	11 [8–15]	124	14 [10–17]	123	13 [10–16]	120	13 [10–17]			
MPAP (mmHg)	Placebo	106	28 [22–36]	114	27 [21–33]	110	29 [23–34]	108	30 [26–34]	104	29 [24–34]	0.15	− 1.03 (0.63)	0.11
	Iloprost	110	29 [24–37]	119	26 [20–32]	121	27 [22–32]	121	30 [25–34]	114	30 [25–36]			
PCWP (mmHg)	Placebo	100	19 [15–23]	109	18 [13–22]	106	17 [14–22]	105	17 [14–22]	90	17 [12–20]	0.12	0.11 (0.52)	0.83
	Iloprost	105	20 [15–25]	116	18 [14–22]	114	17 [14–21]	115	17 [14–21]	101	18 [14–22]			
CI (L·min⁻¹·m⁻²)	Placebo	105	2.00 [1.71–2.47]	114	2.15 [1.77–2.61]	109	3.00 [2.57–3.59]	103	2.79 [2.22–3.37]	95	2.95 [2.54–3.60]	0.88	0.17 (0.08)	0.04
	Iloprost	110	2.14 [1.77–2.69]	121	2.48 [2.02–3.05]	121	3.24 [2.73–4.13]	118	2.90 [2.28–3.61]	113	2.94 [2.46–3.64]			
SVI (mL·m⁻²)	Placebo	105	33 [26–43]	114	33 [27–42]	109	33 [29–39]	103	30 [24–37]	95	32 [27–41]	0.98	1.73 (1.09)	0.12
	Iloprost	110	36 [27–45]	121	35 [28–46]	121	34 [29–44]	118	32 [25–39]	113	33 [27–39]			
SVRI (dyn·sec⁻¹·cm⁻⁵·m⁻²)	Placebo	105	2352 [1807–2997]	112	2293 [1908–2875]	108	1503 [1175–887]	102	1754 [1391–2374]	95	1659 [1312–1999]	0.35	− 138 (58)	0.02
	Iloprost	109	2406 [1782–2851]	120	2004 [1536–2576]	118	1362 [1054–1759]	118	1713 [1250–2270]	111	1507 [1224–2014]			
PVRI (dyn·sec⁻¹·cm⁻⁵·m⁻²)	Placebo	99	382 [227–582]	108	368 [246–527]	103	274 [181–401]	100	387 [251–486]	87	342 [207–488]	0.96	− 40.1 (18.6)	0.03
	Iloprost	102	341 [207–566]	114	258 [178–434]	111	231 [160–325]	113	348 [218–496]	99	331 [249–448]			
PVRI/SVRI	Placebo	100	0.18 [0.11–0.23]	107	0.16 [0.11–0.25]	104	0.18 [0.12–0.26]	103	0.20 [0.13–0.29]	89	0.21 [0.14–0.29]	0.78	− 0.02 (0.01)	0.06
	Iloprost	103	0.15 [0.10–0.24]	113	0.15 [0.09–0.21]	109	0.17 [0.13–0.25]	114	0.21 [0.15–0.28]	99	0.19 [0.14–0.26]			
SvO₂ (%)	Placebo	108	77 [72–83]	113	79 [72–85]	114	80 [74–85]	114	76 [71–85]	99	71 [64–77]	0.11	1.44 (0.76)	0.06
	Iloprost	112	77 [71–83]	119	81 [74–85]	122	83 [74–87]	120	77 [70–82]	104	73 [66–78]			

T1 = baseline (after induction of anesthesia), T2 = just prior to extracorporeal circulation, T3 = after sternal closure, T4 = one hour after admission to the ICU; T5 = six hours after admission to the ICU

P_{T5} = exploratory P-value of the intergroup comparison at T5 (Wilcoxon-Mann-Whitney test); treatment effect = difference of the means iloprost - placebo over repeated times from T2 to T5

Hemodynamic data were analyzed using an explanatory intergroup comparison six to 12 hr after admission to the ICU (T5). In addition, hemodynamic parameters were modelled over time assuming that the parameters were normally distributed. Results of linear mixed models with treatment and time (factor with repeated measurements at T2, T3, T4, and T5, i.e., just prior to and 30 min after end of ECC, one hour and six to 12 hr after admission to the ICU, respectively) as fixed effects and the baseline parameter value after induction of anesthesia (T1) as covariable are provided

CI =cardiac index; ECC = extracorporeal circulation; HR = hazard ratios; ICU = intensive care unit; IQR = interquartile range; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVRI/SVRI = pulmonary/systemic vascular resistance index; SE = standard error; SVI = stroe volume index; SvO₂ = mixed venous oxygen saturation
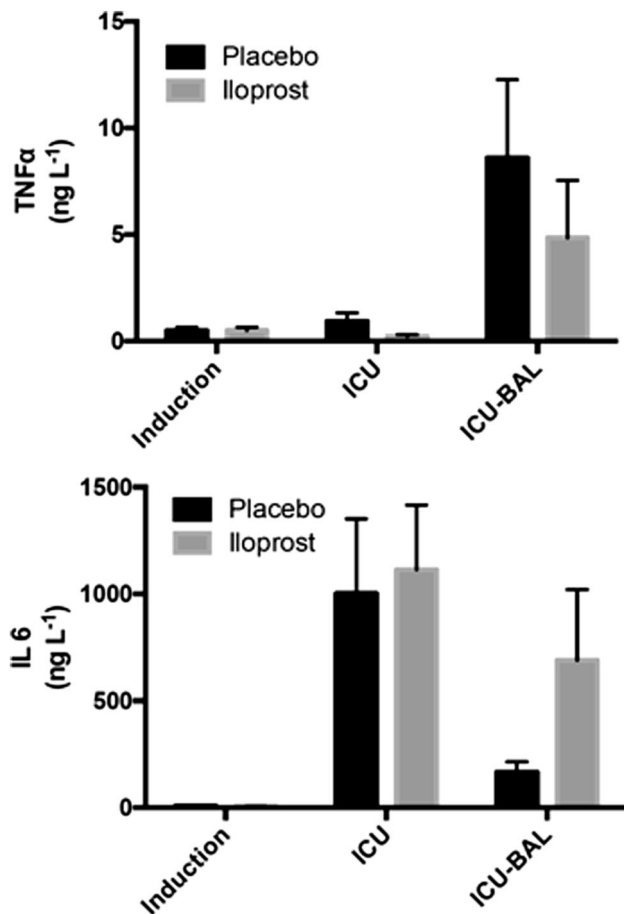
Fig. 4 Perioperative inflammatory profile as assessed by the serum concentration of tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) after induction of anesthesia and six to 12 hr after admission to the intensive care unit (ICU). Moreover, levels of IL-6 and TNF-α are shown that were determined in bronchoalveolar lavage (BAL) fluid (obtained with fibreoptic bronchoscopy six to 12 hr after admission to the ICU). Data were available for 110, 113, and 88 patients in the placebo group, and for 118, 114, and 91 patients in the iloprost group after anesthesia induction, after admission to the ICU and for BAL, respectively. Data are presented as means + SEM

Perioperative inflammation

Serum and BAL levels of pro-inflammatory cytokines were available for 110, 113, and 88 patients in the placebo group, and for 118, 114, and 91 patients in the iloprost group after anesthesia induction, after admission to the ICU, and for BAL, respectively. These values were comparable in the two groups (Fig. 4).

Safety endpoints

Both groups had a comparable incidence of the four pre-specified safety endpoints (Table 4). Likewise, the total

number of all adverse events, deaths, and other serious adverse events did not differ significantly between groups.

Exploratory analyses

In the iloprost group, significantly more patients responded to the first inhalation with a decrease in mPAP of ≥ 20% than in the placebo group (38 *vs* 21, P = 0.01). In the subgroup of the responders, iloprost did not reduce ventilation times (observed change, − 85 min; 95% CI, − 285 to 620; unadjusted P = 0.68; adjusted P = 0.70).

Iloprost levels were determined in all 107 patients included in Düsseldorf (n = 52 receiving placebo, n = 55 receiving iloprost). In the placebo patients, median [IQR] iloprost levels were below the detection limit, whereas the patients receiving iloprost had levels of 72 [52–111] pg·mL^{-1}.

In the subgroup of patients in which the iloprost inhalation resulted in serum levels ≥ the median of all patients (27/55 = 49%), ventilation times were significantly reduced by 253 min compared with the placebo group (95% CI, − 620 to − 5; P = 0.045).

Discussion

In the present study, the prophylactic inhalation of iloprost failed to improve meaningful clinical outcomes in patients with an increased risk of perioperative RV failure undergoing elective open-heart surgery.

Up to now, this is one of the largest multicentre studies and one of the few prospective randomized-controlled trials addressing the perioperative management of PH and associated RV failure in cardiac surgery. We specifically included a high-risk population, illustrated by the baseline characteristics of the included patients and confirmed by an observed 90-day mortality of approximately 15%.

Inhaled iloprost significantly improved systemic hemodynamics by reducing pulmonary vascular resistance and unloading the RV in patients with PH undergoing cardiac surgery.[9,14] While these beneficial hemodynamic effects could be partly confirmed in the present study, they were subtle and did not translate into an improvement of any meaningful clinical outcome. This is in agreement with the findings of a recent meta-analysis in which the use of aerosolized vasodilators improved RV performance but was unable to affect major and clinically relevant outcomes.[12]

Several factors may have contributed to the documented lack of efficacy. First, the observed postoperative ventilation times were considerably shorter than anticipated. This was probably due to fundamental changes in clinical practice of the participating ICU's

Table 4 Safety endpoints

		Placebo (n = 122)	Iloprost (n = 130)	P value
Pre-specified safety endpoints				
Re-thoracotomy for bleeding	n (%)	3 (2.5)	3 (2.3)	1.00
Intracranial hemorrhage	n (%)	0 (0.0)	0 (0.0)	1.00
Ischemic stroke	n (%)	4 (3.3)	4 (3.1)	1.00
Pneumonia	n (%)	16 (13.1)	15 (11.5)	0.71
Adverse events				
All adverse events	n	530	572	n.a.
Death				0.94
Intraoperative	n (%)	0 (0.0)	1 (0.8)	
Before extubation	n (%)	10 (8.2)	8 (6.2)	
After extubation	n (%)	6 (4.9)	7 (5.4)	
After discharge	n (%)	1 (0.8)	2 (1.5)	
Other serious adverse events				
All*	n	94	113	n.a.
Cardiac	n	41	36	n.a.
Infections	n	12	21	n.a.
Respiratory	n	7	18	n.a.
Nervous system	n	10	11	n.a.
Others	n	24	27	n.a.

*Without death

Data are presented as absolute numbers with the percentage (%) of the patients within each group. Categorical variables were compared by means of the Fisher's exact test

n.a. = not available

since the observations upon which the power analysis was based had been made.

Second, the optimal dose of inhaled iloprost in the perioperative setting is still unknown. For the chronic treatment of PH in spontaneously breathing patients, doses of 2.5–5 μg/inhalation are recommended.[30] While exact dose-response relationships for iloprost in ventilated patients are not available, several authors reported significant hemodynamic effects for doses of 20–25 μg areosolized iloprost per inhalation.[9,14] For inhaled milrinone, it has recently been shown that up to 60% of the initially nebulized dose is lost before it reaches the end of the endotracheal tube.[31] We therefore opted for a dose of 20 μg that was several times higher than the effective dose in spontaneously breathing patients and with which we obtained blood levels that have been reported to be in the therapeutic range.[32] The dose of 20 μg resulted in short-term hemodynamic improvements in our patients but was probably still too low to achieve sustainable effects. This is also suggested by the observation of significant effects in the subgroup of patients in which the iloprost inhalation resulted in higher than median blood levels. Future studies are needed to explore dose-response relationships in cardiac surgical patients in the perioperative setting.

Third, the "half-life" of pulmonary vasodilating effects is approximately 21–25 min,[32] necessitating six to nine repetitive iloprost inhalations per day in the treatment of chronic PH.[30] This duration of action was likely too short to cover the entire time span of ECC and to obtain pharmacologic effects lasting beyond the immediate perioperative period. It remains unknown whether continuing iloprost nebulizations in the postoperative period would have resulted in more favourable outcomes.

Fourth, while the efficacy of inhaled iloprost has been proven in patients with pulmonary arterial hypertension and in chronic thromboembolic PH,[30] the vast majority of our patients suffered from PH due to left heart disease, i.e., secondary to systolic/diastolic left ventricular dysfunction and/or valvular disease. Pulmonary vasodilators increase pulmonary venous return, which can potentially overwhelm a failing ventricle.[33] Nevertheless, pulmonary capillary wedge pressures in our study patients were not indicative for such a counterproductive mechanism, a finding recently reported also in medical patients with PH due to left heart failure.[34]

Fifth, although focusing on a high-risk population, the inclusion and exclusion criteria may have been too liberal (resulting in only 60% of the included patients suffering from PH and having a NYHA class ≥ III). Notably,

iloprost appeared to have a greater effect in patients with a EuroSCORE > 10. Further studies should therefore target patients with an extremely high surgical risk and poor functional state due to PH.

Sixth, unbalanced pulmonary vasoconstriction is only one pathophysiologic mechanism contributing to post-ECC cardiopulmonary dysfunction. In cardiac surgery, numerous triggers of postoperative organ dysfunction have been identified in which prostacyclins have no or only an ancillary role, e.g., coronary hypoperfusion/ischemia, systemic inflammatory response, valvular dysfunction, atelectasis, volume overload etc. Hence, re-enforcing the PGI_2 pathway by nebulization of iloprost would simply be unable to target all the various etiologies underlying prolonged ventilator dependency on ICU or other "hard" outcome parameters. Similar considerations have been brought forward to explain why, in two multicentre trials, neither endothelin blockade nor inhaled milrinone prevented RV failure in high-risk cardiac surgery,[6,8] and why, in a recent meta-analysis, inhaled vasodilators in general failed to improve clinically relevant outcomes.[12]

While we failed to show a benefit from the routine prophylactic application of inhaled iloprost in cardiac surgery, this should not invalidate the established use of nebulized PGI_2 as a rescue treatment for perioperative PH and associated RV dysfunction.[35]

Lastly, we did not observe an increased incidence of adverse effects after perioperative iloprost inhalation. Prostacyclins are well-known inhibitors of platelet aggregation that can be used for therapeutic purposes.[36,37] Therefore, it has been argued that PGI_2 nebulization could inhibit platelet aggregation and hence increase the risk of intra- and postoperative bleeding. In fact, PGI_2 inhalation in cardiac surgical patients impairs platelet aggregation *in vitro*.[38] The majority of clinical trials documented no impact on surgical bleeding though.[38,39] Our data support these latter findings, as iloprost inhalation was not associated with an increased incidence of re-thoracotomy for bleeding or hemorrhagic stroke.

After iloprost inhalation, a significant spill-over into the systemic circulation can reduce systemic vascular resistance and eventually arterial hypotension.[32] Nevertheless, systemic vasodilating effects of inhaled iloprost are normally counteracted by a more pronounced effect on pulmonary vascular resistance and consecutive increases in cardiac output,[9,32] which was also observed in our study. Hence, iloprost inhalation was not associated with arterial hypotension, which is underlined by the fact that both treatment groups did not differ notably with respect to vasopressor requirements.

We acknowledge that our study suffers from several limitations. First, the study was only powered for a single primary outcome. Hence, the majority of observations concerning secondary and safety outcomes should be interpreted with caution. Second, the use of rescue iloprost in the placebo group could have "diluted" the treatment effect and may confound the interpretation of the results. Nevertheless, the use of inhaled iloprost as rescue medication was virtually identical in both groups, most probably confirming the lack of effectiveness. Moreover, after eliminating the patients having received rescue iloprost from the statistical analysis, the primary outcome remained virtually unchanged (data not shown). Third, owing to the fact that the present study was a pragmatic clinical effectiveness trial, there was no ECC weaning protocol and no mandatory hemodynamic treatment algorithm. Details of patient management were not documented on the clinical record forms. Hence, we are unable to report intercentre differences in patient management. Nevertheless, we suggest that the primary outcome was not subject to significant intercentre variability in management. No difference in outcome could be detected when stratifying the primary analysis for the different centres ($P = 0.35$) or for the EuroSCORE and the centre ($P = 0.37$).

Also the performance of echocardiography was left at the discretion of the investigators. Detailed echocardiographic data were not documented in the case record forms (except for signs suggestive of RV failure), and echocardiography files were not centrally evaluated.

In conclusion, this prospective randomized controlled multicentre trial on the prophylactic inhalation of iloprost in patients undergoing high-risk cardiac surgery with ECC did not show a reduction in postoperative ventilation time and suggests neither a clinically meaningful benefit nor a clinically meaningful increased incidence of adverse events.

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