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PROTECTIVE EFFECTS OF ILOPROST ON CARDIOPULMONARY BYPASS INDUCED LUNG INJURY

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ABSTRACT:

Purpose: Iloprost, a prostacyclin analogue with a prolonged plasma half-life, has beneficial effects on chronic pulmonary hypertension, but its effects on acute lung injury are not well known. We investigated whether iloprost infusion through the pulmonary artery during aortic cross-clamping prevents pulmonary dysfunction after cardiopulmonary bypass (CPB) by measuring inflammatory cytokine levels (IL-1β, IL-6, IL-8, TNF-α), white blood cell (WBC) counts from the left atrium and lung biopsies.

Materials and Methods: Twenty elective patients undergoing coronary bypass surgery were divided into two groups. The study group (n=10) received iloprost infusion (2 μg/kg/min) during CPB via a catheter inserted into the pulmonary artery. The control group (n=10) underwent a standard CABG operation. Broncho-alveolar lavage (BAL), respiratory function tests, blood gas measurements, interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α) and white blood cell counts were determined. Blood samples were collected from the left atrium through the right superior pulmonary vein before commencing CPB (T1), at the 5th (T2) and 20th minutes (T3) of aortic cross-clamping, and after weaning from CPB (T4). Blood for WBC counts and lung biopsy specimens were collected after weaning from bypass.

Results: In the study group FEV1/FVC and pCO_2 levels were better than those in the control group. There was a greater inflammatory cellular increase in the BALs of the control group. IL-1β levels at T4 were significantly lower in the study group (0.87 ± 0.16 vs. 1.17 ± 0.24, p

Conclusion: Iloprost infusion via a catheter introduced through the pulmonary artery during the aortic cross-clamp period decreases the inflammatory response and acute lung injury after CPB.

Key words: Cardiopulmonary By-pass, Lung Injury, Prostaglandin Analogue

ILOPROST'UN KARDİYOPULMONER BY-PASS İLE İNDÜKLENEN AKCİĞER HASARINA KARŞI KORUYUCU ETKİLERİ

ÖZ:

Amaç: Uzun yarı ömürlü bir prostosiklin analoğu olan Ilomedin'in, kronik pulmoner hipertansiyon üzerindeki olumlu etkileri bilinmekle beraber, akut akciğer hasarı üzerine olan etkileri tam olarak arastırılmamıstır. Iloprost'un kardiyopulmoner by-pass nedeniyle gelisen akut akciğer hasarına karsı koruyucu etkinliğinin var olup olmadığı, kardiyopulmoner by-pass esnasında pulmoner arterden verilerek, sol atriumdan ve akciğer biopsilerinden alınan inflamatuvar sitokin seviyelerine (IL-1β, IL-6, IL-8, TNF-α) ve beyaz küre sayımına bakılarak arastırılmıstır.

Gereç ve Yöntem: Koroner by-pass cerrahisine alınacak 20 hasta iki gruba bölünmüstür. Çalışma grubunda (10), kardiyopulmoner by-pass (KPB) esnasında pulmoner arterden bir kateter yoluyla 2 μg/kg/min dozunda Iloprost infüzyonu yapılmıstır. Kontrol grubunda (10) operasyon standart olarak devam etmistir. Bronko-alveolar lavaj (BAL), solunum fonksiyon testleri, kan gazı analizleri, interlökin-1β (IL-1β), interlökin-6 (IL-6), interlökin-8 (IL-8) and tümör nekroz faktör alfa (TNF-α) çalısma kriterleri olarak belirlenmistir. Kan örnekleri üst sağ pulmoner venden, KPB'a baslanmadan önce (T1), kross-klempin 5. dakikasında (T2), 20. dakikasında (T3) ve KPB'tan ayrıldıktan sonra (T4) alınmıstır. Beyaz küre sayımı için kan örneklemesi ve akciğer biopsileri KPB'tan sonra toplanmıstır.

Bulgular: Çalışma grubunda FEV1/FVC ve pCO2 değerleri daha iyi olarak bulundu. Kontrol grubunun BAL'larında daha çok inflamatuvar hücreye rastlanmıstır. T4 zamanında IL-1β seviyeleri, kontrol grubuna oranla belirgin olarak düsük bulunmustur (0.87 ± 0.16 ile 1.17 ± 0.24, p

Sonuç: Aort kros klemp esnasında pulmoner arterden bir kateter yoluyla yapılan Iloprost infüzyonu, KPB nedeniyle ortaya çıkan inflamatuvar cevabı ve akut akciğer hasarını azaltabilmektedir.

Anahtar Kelimeler Kardiyopulmoner By-Pass, Akciğer Hasarı, Prostoglandin Analoğu

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INTRODUCTION

Post-pump syndrome was identified early following the development of cardiopulmonary bypass (CPB) in the 1950s and is characterized by increased alveolo-arterial gradient (A-aDO2) and intrapulmonary shunt, decreased pulmonary compliance, increased pulmonary vascular resistance and permeability,[1,2] and is related to the systemic inflammatory response associated with CPB.[3] Ischemia-reperfusion injury is the major cause of this syndrome but contact of blood with the nonphysiological surface of the circuit and endotoxemia are also implicated in a cascade of events including activation of the complement system, induction of adhesion molecules, cytokine release, and neutrophil activation. The final pathway of this inflammatory process leads to activation and dysfunction of the endothelium.[3,4] Other factors that might affect lung vascular injury include surgical trauma[5,6] and the use of blood products increasing the risk of transfusion-related lung injury.[7,8]

About 25% of patients who do not present any severe cardiac dysfunction following open heart surgery are reported to have a significant respiratory impairment for at least one week after the operation.[9] The most significant proportion of this impairment is due to CPB, which usually leads to excessive interstitial pulmonary edema and subsequent abnormal gas exchange. Abnormal gas exchange together with an acute pulmonary injury and concomitant severe inflammation following CPB can subsequently lead to various clinical symptoms ranging from fever and productive cough, to respiratory failure requiring prolonged mechanical ventilation, and even to acute lung injury (ALI), or, ultimately, to acute respiratory distress syndrome (ARDS).[10-12]

Prostacyclin (PGI2) is an endogenous prostaglandin derived from the arachidonic acid metabolism through the cyclooxygenase pathway in the vascular endothelium. PGI2 binds to a Gs-protein–related receptor, which when activated increases cyclic adenosine monophosphate (cAMP) concentration, activating a protein kinase A to decrease free intracellular calcium concentration. Increases in cAMP levels lead to protection of endothelial functions and improvement of pulmonary functions during ischemia-reperfusion (I/R). Intracellular cAMP levels and prostacyclin production decrease during ischemia, giving rise to considerable deterioration of vascular functions.[13-15] There are few studies establishing the effects of prostacyclins in preventing acute lung injuries. The aim of this study was to determine the effects of a prostacyclin analogue on cardiopulmonary bypass induced lung injury.

MATERIALS AND METHODS

This was a prospective study, approved by the local Ethical Committee and performed at Gazi University Medical Faculty, where about 550 open heart procedures are performed per year.

Patients: Twenty patients scheduled for elective coronary artery bypass surgery were enrolled in the study and written consent was obtained from all patients. Physical examinations and laboratory evaluations were performed. Following completion of the

respiratory function tests, blood gas analyses, and chest radiograms, all patients were referred to a chest consultant before surgery. Age over 75, additional cardiac pathologies, chronic obstructive/restrictive pulmonary disease, previous cardiac surgery, ejection fraction below 35%, emergency surgery, systemic diseases (renal failure, hepatic insufficiency, hematologic diseases), cerebrovascular disease, and previous malignancy history were the exclusion criteria. Patients were divided into two equal groups. The study group received iloprost infusion through the pulmonary artery during the aortic cross-clamping period (n=10). The control group received no medication (n=10). After premedication with diazepam (10 mg), anesthesia was induced with thiopental (5 mg/kg) and fentanyl (0.05 μg/kg). Muscular relaxation was achieved with pancuronium bromide (0.1 mg/kg). Anesthesia after intubation was maintained with O_2/N_2O: 50%-50% and 1-1.5 MAC isoflurane.

Operative Technique: After median sternotomy the left thoracic cavity was opened in order to harvest the left internal thoracic artery. Heparinization (300 IU/kg), and standard cannulation techniques through the ascending aorta and right atrium were used to establish the CPB circuit. CPB was performed with a membrane oxygenator and non-pulsatile pump. After the institution of CPB, the patients were cooled to 28 °C and CPB flow was adjusted to 2.2 l/min/m². The management of myocardial protection was identical in the two groups. Cardiac arrest was achieved with cold blood cardioplegia and repeated every 20 min. Patients in the study group received iloprost infusion (2 μg/kg/min) through a catheter introduced into the pulmonary artery. Infusion was continued during the aortic cross-clamp period. After cardiac arrest distal anastomoses were performed first. With the completion of the last anastomosis warm blood cardioplegia was infused and the aortic cross-clamp was removed. After the completion of proximal anastomoses the patients were weaned from CPB. The aortic cross-clamp and total cardiopulmonary bypass periods were recorded. Following the decanulation procedure, controls for haemostasis were completed and the sternum was closed in the usual manner.

Measurements: Blood samples for determination of IL-1β, IL-6, IL-8, and TNF-α levels were collected just before commencing CPB (T1), at the 5th (T2) and 20th min (T3) of aortic cross-clamping, and after weaning from CPB (T4) through the right superior pulmonary vein. BALs of patients were collected before and after weaning from CPB. Respiratory function tests and blood gas analyses were done before the operation and on the 7th postoperative day before discharge. Blood for WBC counts was collected just before commencing CPB and after removal of the aortic cross-clamp via the right superior pulmonary vein. Lung biopsy specimens were collected after weaning from CPB.

IL-1β, IL-6, IL-8, and TNF-α levels were measured using an enzyme-linked immunosorbent assay and immunoradiometric assay (Biosource International, Inc. USA). BALs were centrifuged (Shandon Cytopsin 3) for 5 min at 800 rpm and aggregates were stained with Papa-Nicolo and hematoxylin-eosin for microscopic analysis. Lung biopsy specimens were formalin fixed, paraffin-embedded, 0.4 micron thick sliced, and stained with hematoxylin-eosin for light microscopic analysis. Blood gas analyses and respiratory function tests were evaluated for pCO_2 and FEV1/FVC values.

STATISTICAL ANALYSIS

SPSS 13.0 for Windows was used for analysis. Values were reported as mean ± standard error of the mean (SEM). The Wilcoxon test was used to compare data within groups and Mann-Whitney U test to compare data for differences between the two groups.

RESULTS

Patient demographics and perioperative data are presented in Table 1. There were no differences between the groups in terms of risk factors for coronary artery disease and perioperative mortality and morbidity. There were also no hospital mortality, pulmonary insufficiency, or neurological complications. Surgical operations were performed by the same team. No significant differences were seen with regard to CPB time, aortic cross-clamp time, internal thoracic arteries used, or number of coronary bypass grafts.

Absolute results of FEV1/FVC, WBC counts, pCO_2, and BAL inflammatory cell counts are listed in Table 2. WBC counts were similar before commencing CPB. Although significant increases were detected in both groups at T4, the increase in the study group was lower. Preoperative pulmonary function tests and blood gas analyses revealed similar FEV1/FVC and pCO_2 values. pCO_2 controls on the 7th postoperative day showed lower values in the study group. Lung biopsy specimens also showed less inflammation in the study group (Figure 5).

Table 1. Demographics, Clinical Characteristics, and Operative Data.

Characteristics	Study (n=10)	Control (n=10)
Age (y)	63.9 ± 6.8	62.7 ± 7.8
Sex (M/F)	7/3	7/3
Actively smoking (n)	4	3
Non-smoking (n)	6	7
DM (n)	3	3
Preoperative MI (n)	4	3
EF (%)	53.1 ± 8.2	50.5 ± 8.6
Operative Data		
LIMA used for CABG (n)	10/10	10/10
CPB time (min)	94.6 ± 25.2	95.3 ± 25.6
Aortic cross-clamp (min)	46.5 ± 14.4	49.9 ± 13.5
Need for IABP (n)	-	-
Perioperative MI (n)	-	-

Values are expressed as numbers, median and range, or means ± SD. *P* values all nonsignificant.

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; MI = myocardial infarction;

EF = ejection fraction; LIMA = left internal mammary artery;

IABP = intra-aortic balloon pump; DM = diabetes mellitus

Table 2. Respiratory, BALc, and WBC data.

	Control Grup	Study Grup	p value
Preoperative FEV1/FVC	86.1 ± 7.7	85.9 ± 8.5	0.970
Postoperative FEV1/FVC	72.4 ± 4.6[a]	82.5 ± 8.5	0.029[b]
Preoperative pCO_2	28.2 ± 1.8	27.0 ± 4.4	0.345
Postoperative pCO_2	33.8 ± 1.7[a]	29.0 ± 3.7	0.002[b]
Pre-CPB WBC	7484 ± 1364	7368 ± 1635	0.910
Post-CPB WBC	14770 ± 1829[a]	12940 ± 1755[a]	0.031[b]
Pre-CPB BALc	49.5 ± 6.4	46.5 ± 9.6	0.262
Post-CPB BALc	57.0 ± 10.6[a]	49.0 ± 7.8	0.037[b]

[a] $p<0.05$ within groups. [b] $p<0.05$ between groups. Values are mean ± SD.

pCO_2 = carbon dioxide tension; BALc = broncho-alveolar lavage inflammatory cell counts; WBC = white blood cell

Values of cytokines are listed in Table 3.

Table 3. Values of cytokines IL-1β, IL-6, IL-8, and TNF-α derived from right superior pulmonary veins of 20 patients undergoing CABG before commencing CPB (T1), at the 5th minute (T2) and 20th minute of aortic cross-clamping (T3), and after weaning from CPB (T4).

	T1	*T2*	*T3*	*T4*
IL-1β				
Control	0.56 ± 0.12	0.71 ± 0.14[a]	0.78 ± 0.17[a]	1.17 ± 0.24[a]
Study	0.63 ± 0.12	0.58 ± 0.21	0.63 ± 0.18	0.87 ± 0.16[a,b]
IL-6				
Control	23.7 ± 10.0	30.2 ± 13.0[a]	35,1 ± 12,8[a]	120,2 ± 58,2[a]
Study	27,2 ± 11,4	37,9 ± 19,2[a]	39,0 ± 16,4[a]	84,0 ± 22,2[a,b]
IL-8				
Control	23,9 ± 8,3	31,3 ± 9,2[a]	41,3 ± 13,8[a]	131,2 ± 38,6[a]
Study	27,3 ± 7,3	25,9 ± 6,0	0,2 ± 9,1[a,b]	81,5 ± 27,1[a,b]
TNF-α				
Control	45,6 ± 10,0	51,4 ± 10,2[a]	55,4 ± 10,6[a]	111,4 ± 34,3[a]
Study	49,4 ± 12,9	48,0 ± 18,3	47,2 ± 12,9	78,8 ± 15,9[a,b]

[a]$p<0.05$ within groups. [b]$p<0.05$ between groups. All values are mean ± SD.

IL-1β Levels: There were no differences at T1. At T2 also levels did not differ between the groups. Increases at T3 were greater in the control group but the difference was not statistically significant ($p=0.069$). In the study group, no significant difference was observed at T1, T2, and T3 but at T4 levels were significantly higher than they were at T1 ($p=0.005$, $p<0.05$). In the control group a time relevant increase was observed at T2, T3, and T4 ($p<0.05$). Although at T4 levels were higher than those at T1 in both groups, the increase in the study group was significantly lower than that in the control group ($p=0.004$, $p<0.05$) (Figure 1).

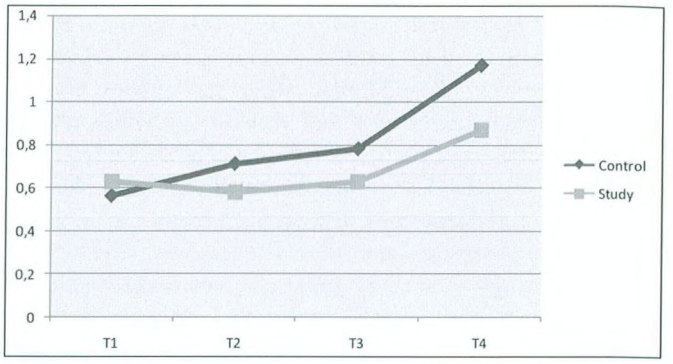

Figure 1. Concentrations of IL-1β from right superior pulmonary vein blood before CPB (T1), at 5 min (T2) and 20 min (T3), and after weaning from CPB (T4). Values are means.

IL-6 Levels: T1, T2, and T3 levels were similar between the groups. Levels at T2, T3, and T4 were all significantly higher than those at T1 within both groups. The increase at T4 in the study group was significantly lower than that in the control group ($p<0.05$) (Figure 2).

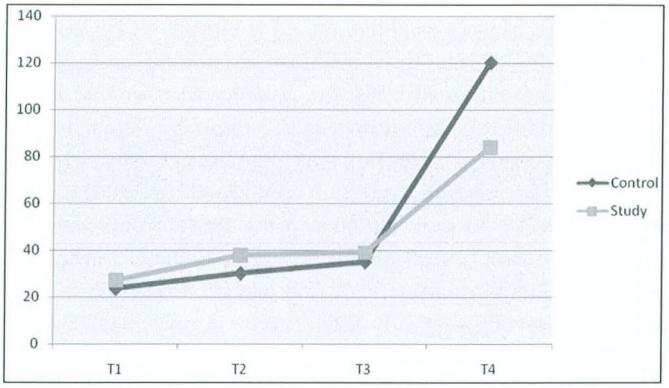

Figure 2. Concentrations of IL-6 from right superior pulmonary vein blood before CPB (T1), at 5 min (T2) and 20 min (T3), and after weaning from CPB (T4). Values are means.

IL-8 Levels: No difference was observed at T1 and T2 between the groups. In the study group, while there were no differences at T2, the increases at T3 and T4 were statistically significant. Elevations in the control group were all higher according to T1. T3 and T4 levels in the control group were significantly higher than those in the study group ($p<0.05$) (Figure 3).

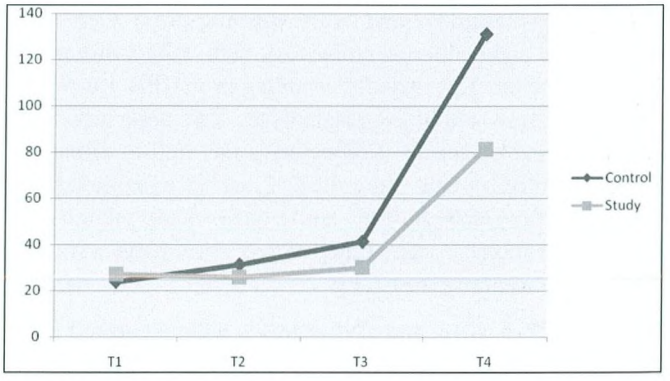

Figure 3. Concentrations of IL-8 from right superior pulmonary vein blood before CPB (T1), at 5 min (T2) and 20 min (T3), and after weaning from CPB (T4). Values are means.

TNF-α Levels: T1 levels were similar between the groups. T2 and T3 levels in the study group showed no significant difference. Moreover, a non-significant decrease was observed at T2 and T3 in the study group. In the control group, at T2 and T3 there were marked increases, which were scientifically significant. T4 levels in the study group were also significantly lower than those in the control group (Figure 4).

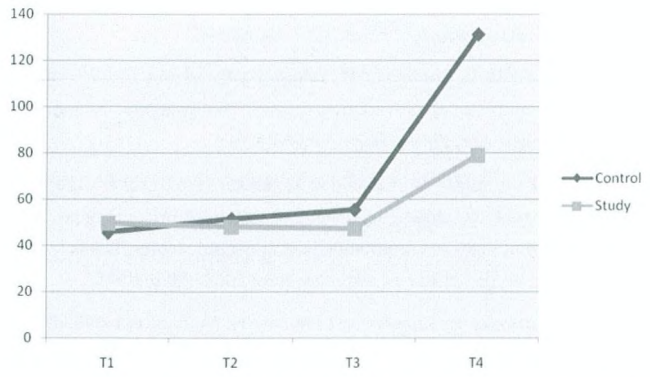

Figure 4. Concentrations of TNF-α from right superior pulmonary vein blood before CPB (T1), at 5 min (T2) and 20 min (T3), and after weaning from CPB (T4). Values are means.

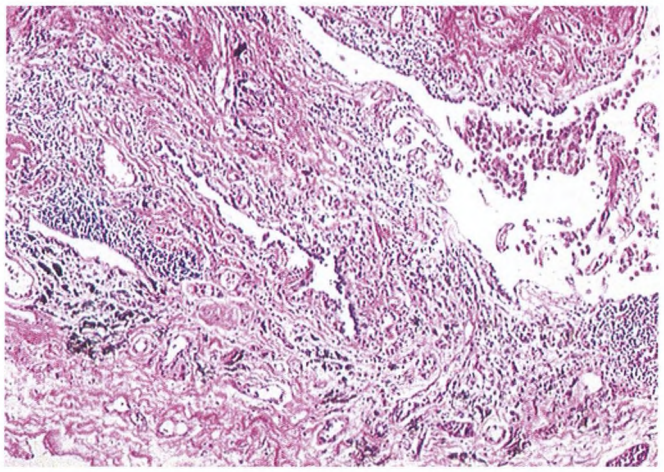

Figure 5. Lung biopsy specimens of control group revealing parenchymal infiltration with lymphocytes, forming aggregates and foamy histiocytes at alveolar spaces.

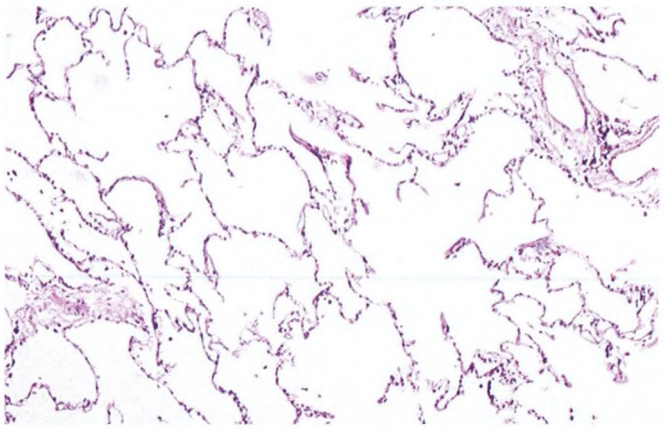

Figure 5. Less inflammation in study group.

DISCUSSION

Pulmonary dysfunction after cardiac surgery involving CPB remains an important clinical challenge despite refinements and improvements in the technique and materials used. Attention has been given to off-pump surgery, reducing CPB time, minimizing the extracorporeal surface area, and use of "biocompatible" surfaces as those of heparin-coated and material independent sources of blood activation, and better results have been reported.[16,17] CPB, essential to most cardiac operations, is suspected to cause a systemic inflammatory response syndrome (SIRS) partly caused by the contact of blood with foreign surfaces of the heart-lung machine. In this setting the development of SIRS has been well established.[18,19] Moreover, the heart and lungs were shown to add to the inflammatory response by releasing cytokines and favoring cellular adhesion during postischemic reperfusion.[20,21] All these result in endothelial injury, increased microvascular permeability, decreased pulmonary compliance, and pulmonary dysfunction.

The conventional CPB technique with atrial and aortic cannulas and an artificial oxygenator has been shown to be associated with a considerable increase in the levels of proinflammatory cytokines IL-6 and IL-8 during the pulmonary passage after declamping of the aorta.[34] Although there have been many studies on cytokine release such as TNF-α,[22,23] IL-1β,[24] IL-6,[25] and IL-8,[26] the literature on TNF-α levels during CPB is controversial[27], and TNF-α has been found to be systematically elevated during and after CPB[18,28], particularly after congenital cardiac surgery [28]. Others observed no increase during cardiac surgery[29].

Prostacyclin regulates the intracellular concentration of cAMP by binding to a Gs-protein related receptor, which when activated increases intracellular cAMP concentrations and plays an important role in the maintenance of vascular function, including pulmonary vasodilatation,[30] inhibition of platelet aggregation,[31] down regulation of neutrophil adhesions,[32] and scavenging of free radicals.[33] However, when endothelial cells are exposed to ischemia-reperfusion, tissue cAMP levels in the lung decrease.[13] This alters the ability of lungs to release endogenous prostacyclin,[35] and impairs prostacyclin de novo synthesis.[15,36] Thus, including exogenous prostacyclin during the aortic cross-clamp period may help in preventing ischemia-reperfusion induced lung injury.

In this study, significant concentration increases in cytokines were observed during CPB. Although cytokine levels increased in both groups, alterations in the study group were significantly lower during and after removal of the aortic cross-clamp. Under CPB conditions and aortic cross-clamping the heart and lungs are excluded from circulation. Only blood supply to the lungs continues via bronchial arteries. After release of the aortic cross-clamp, reperfusion of the heart leads to cardiac inflammatory response, as evidenced by the transcardiac release of ILs and activated cellular adhesions.[21] In a study by Massoudy et al.,[34] the same reaction was shown

for the lungs. Our results also correlated with those, revealing an increase in cytokine levels, particularly after the release of the aortic cross-clamp.

Some reports have shown beneficial effects of prostacyclin analogue in pulmonary ischemia and reperfusion injury when used before ischemia. In these studies, iloprost associated protection was attributed to attenuation of platelet aggregation,[31,15] preventing neutrophil sequestration,[37] and improving microvascular blood flow distribution.[39] In contrast, Hooper et al.[38] and Matsuzaki et al.[40] showed no benefit by administration of prostacyclins before ischemia. Kawashima et al.[41] also reported beneficial results with iloprost against lung injury when administered before reperfusion, but not when administered before ischemia, and commented that ischemia duration's exceeding the half-life of iloprost, which is 30 min[42], may have limited the protective efficacy of the drug when given before ischemia. Such an effect was avoided by administering iloprost during the ischemia period in our study.

Suzuki et al. demonstrated that continuous pulmonary perfusion during CPB prevented lung injury and neutrophil sequestration.[42] Neutrophil sequestration in the pulmonary capillary bed during CPB gives rise to pneumocyte damage and endothelial injury. Those effects have also been shown in humans. In the present study, WBC counts before commencing CPB and after removal of the aortic cross-clamp were compared. The control group's WBC levels were significantly higher than those of the study group. FEV1/FVC levels decreased more in the control group, revealing an obstructive pattern that may be caused by excessive interstitial fluid and airway edema. Moreover, the significant pCO_2 increase in the control group supported our hypothesis that iloprost may have protective effects on CPB induced lung injury. Light micrographs of lung biopsy specimens showed slight inflammation in the study group, whereas there was marked inflammation in the control group's micrographs.

In conclusion, there is a considerable increase in cytokine levels during aortic cross-clamping and soon after removal of the cross-clamp. Inflammatory cell retention is also detected both in blood and BAL samples. These show similarity with previously described post-bypass pulmonary dysfunction and neutrophil activation[9,10,19,20]. Infusion through the pulmonary artery during the aortic cross-clamp period decreases inflammatory response, prevents neutrophil sequestration, and ameliorates CPB induced lung injury. Future and wider studies are needed to gain more information about the effects of iloprost.

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