The effect of pentoxifylline on the lung during cardiopulmonary bypass

Abstract Cardiopulmonary bypass (CPB) produces an inflammatory response due to the interaction of blood with a foreign body surface. The lungs are most affected by this inflammatory response. Pentoxifylline (PTX), a phosphodiesterase inhibitor and an inhibitor of leukocyte activation, is used to minimize damage in lungs where leukocytes play an important role. Twenty patients with mitral valve stenosis with planned mitral valve surgery were included in the study. The ten patients receiving pentoxifylline (PTX group) were administered 400 mg PTX orally TID for 3 days preoperatively and, following anesthetic induction, a 300 mg PTX infusion was given. The ten patients receiving no PTX were the control group (CT). Platelet and leukocyte counts, mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), pulmonary vascular resistance (PVR), alveolar-arterial PO2 gradient (AaDO2) were measured just before and after CPB, and 2 h postoperatively. The number of the leukocytes increased in the blood samples drawn 15 min after CPB in both groups and 2 h postoperatively showed no statistical change. The number of platelets had decreased significantly at the end of the CPB in both groups and, 2 h postoperatively, there was a further decrease in the blood count in the control group (P<0.05). There was no significant difference in either the preoperative or postoperative PAP, PAWP, and CI. Pulmonary vascular resistance increased in both groups following the CPB (CT, before: 136±44, after: 177±94 dynes·sec·cm−5; PTX, before: 151±82, after 182±43 dynes·sec·cm−5). Two hours postoperatively, a considerable increase continued in the control group (CT 219±170 dynes·sec·cm−5), while there was an insignificant increase in the PTX group (PTX 193±51 dynes·sec·cm−5) (P<0.05). The alveolar-arterial PO2 gradient increased after the CPB in both groups but a moderate decrease was observed 2 h postoperatively. In lung biopsy specimens taken before and after the CPB, there was marked leukocyte sequestration in the control group, whereas the number of leukocytes was seen to be insignificant in the PTX group (P<0.005). This dosage regimen of PTX inhibits the postoperative increase in PVR and greatly minimized leukocyte sequestration in the lung due to CPB.

Key words Cardiopulmonary bypass · Pentoxifylline · Lung
Introduction

Pulmonary dysfunction after cardiopulmonary bypass (CPB) is described as resulting from activation of the complement system and leukocytes with subsequent leukosequestration [9, 20]. Release of oxygen free radical species by active neutrophils may cause tissue injury by peroxidation of lipids and nucleic acids [33]. Reduction of lung injury may be achieved by inhibiting neutrophil activation. Many drugs, such as steroids, protease inhibitors and free radical scavengers, have been used in an attempt to reduce the organ damage produced by CPB [5, 26, 37]. Pentoxifylline (PTX), a methylxanthine derivative, inhibits in vitro neutrophil activation, including adhesion, and chemotaxis, oxidant release [4, 16, 29]. Pentoxifylline also inhibits the inflammatory action of IL-1 and TNF on neutrophil function [36].

In this study, we examined the effects of PTX on leukocyte sequestration in the lung after CPB and also determined hemodynamic changes after PTX administration.

Patients and methods

Patient population

Twenty patients (11 male, 9 female) undergoing valve replacement gave informed consent for lung biopsy and blood sampling during operations. The protocol was approved by the Human Ethics Committee of the Izmir State Hospital. All patients in the study had mitral valve disease caused by acute rheumatic fever and the following inclusion criteria: a left ventricular ejection fraction greater than 50%, absence of major non-cardiac illness, especially primary pulmonary disease, and no history of the recent use of steroids, non-steroid anti-inflammatory drugs, or theophylline-like drugs. Patients, data are summarized in Table 1. The ten patients in the PTX group were administered 400 mg PTX (Trental) orally TID 3 days before the operation and 300 mg as an intravenous infusion, 5 min after anesthetic induction, before administering heparin. The infusion lasted 15 min. The ten patients in the control (CT) group received no PTX.

Anesthesia protocol

Regular medications were continued up to the morning of the operation. Premedication was by diazepam (5 mg) administered orally the evening before the operation and the same dose was administered 1 h before surgery. Anesthetic induction and maintenance were achieved with fentanyl (10–15 μg/kg), thiopental (1–2 mg/kg), pancuronium bromide (0.1–0.15 mg/kg), oxygen with nitrous oxide (50%), and halothane (0.5–1.0%). A Swan-Ganz catheter was introduced into the pulmonary artery via the internal jugular vein. Neither corticosteroids nor aprotinin was administered before or during the operation. After CPB, dobutamine and dopamine (less than 5 mcg/kg per min) were given if necessary.

Table 1 Patient characteristics and variables pertaining to operation (NS not significant, NYHA New York Heart Association, LVEF left ventricular ejection fraction)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PTX group</th>
<th>CT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>37 ± 11</td>
<td>35 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>5/5</td>
<td>6/4</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Preop LVEF (%)</td>
<td>60 ± 12</td>
<td>62 ± 11</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2 Operative details (CPB cardiopulmonary bypass, AVR aortic valve replacement, TV tricuspid valve, LA left atrial)

<table>
<thead>
<tr>
<th>PTX</th>
<th>CT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min)</td>
<td>212 ± 83</td>
<td>205 ± 75</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>132 ± 54</td>
<td>119 ± 48</td>
</tr>
<tr>
<td>Aortic occlusion time (min)</td>
<td>91 ± 42</td>
<td>87 ± 36</td>
</tr>
<tr>
<td>Concomitant surgical procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>TV annuloplasty</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>LA plication</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>LA trombectomy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lowest temperatures of CPB (°C)</td>
<td>27 ± 1.3</td>
<td>27 ± 1.1</td>
</tr>
</tbody>
</table>

Surgical technique

A pulsatile roller pump was used in all operations. The extracorporeal circuit was primed with a bubble oxygenator (Shiley S-100A). Heparin (3 mg/kg body weight) was infused to maintain an activated clotting time (ACT) of more than 480 s during bypass. Flow rates of 2.4 l/min per were used to maintain a systemic perfusion pressure of 40–60 mmHg. Cold blood cardiopulmonary solution was used in addition to local cooling and moderate general hypothermia (28–32 °C). St. Jude Medical mitral and aortic valves were used. Interrupted single sutures were used to fix the artificial valve to the mitral valve annulus and aortic valve annulus. The concomitant surgical procedures performed in the two groups are indicated in Table 2. Cardiopulmonary bypass was terminated at a core temperature of 36.8–37 °C. The protamine dosage was equal to the heparin dosage, and additional protamine was given when needed to re-establish pre-bypass ACT levels.

Hematology

Blood samples were taken after heparinization, 15 min after CPB and 2 h postoperatively in the Intensive Care Unit (ICU). Leukocytes and platelets were counted with an automatic cell counter.

1 Hoechst-Roussel, Sommerville, N.J., USA
2 Baxter Healthcare Corp., Edwards Division, Irvine, Calif., USA
3 Cobe, Lakewood, Colo., USA
4 Shiley Inc., Irvine, Calif., USA
5 St. Jude Medical Inc., St. Paul, Minn., USA
6 Coulter Co., Dunstable, U.K.
Hemodynamic measurement

Hemodynamic measurements [heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP) and thermodilution cardiac index (CI)] were obtained: A, after infusion of PTX; B, after cessation of CPB plus a period of 15 min of hemodynamic stability, just before administration of protamine hydrochloride; and C, 2 h after the operation, in the ICU. Pulmonary vascular resistance (PVR) was calculated as 79.92×(mPAP-PCWP/CI (U/min)).

Pulmonary function measurement

Arterial blood samples were obtained from the radial artery cannula for blood gas measurements (blood gas system, Stat profile 5 Nova Biomedical). The alveolar-arterial PaO2 gradient was calculated using the alveolar gas equation, assuming a respiratory quotient (RQ) of 0.8:

\[ P_{A\text{O}2} = (P_{F\text{O}2} × (PB_{atm} - SVPH_{2O}))/P_{A\text{CO}2} - (P_{A\text{CO}2} × (1 - P_{F\text{O}2}/RQ)) \]

where \( P_{A\text{O}2} \) is alveolar \( P_{O2} \), \( PB_{atm} \) is barometric pressure, \( SVPH_{2O} \) is saturated vapor pressure of water at 37 °C, and \( P_{A\text{CO}2} \) is alveolar \( P_{CO2} \), which is assumed to be equal to \( P_{CO2} \). All measurements were taken with the patient anesthetized in the supine position. The measurement of the alveolar-arterial \( P_{O2} \) gradient was made at the same time as hemodynamic measurements.

Lung biopsy and histologic examination

After the median sternotomy, a lung biopsy sample was taken from the middle lobe of the right lung before the patients were heparinized and the biopsy side of the lung was sutured. Following decannulation, just before closing the sternum, the pleura was re-opened to take the second biopsy sample 1–2 cm away from the first site and the second biopsy side was sutured again. The heparin had been neutralized by protamine and the ACT had been observed at pre-bypass levels before we took the second biopsy. Lung biopsy materials were fixed in 10% buffered formalin solution. After routine processing, sections were taken 5–6 μm of thickness from paraffin blocks and stained with hematoxylin and eosin. Neutrophil density was measured by grid counting to determine the number of neutrophils falling on points of a lattice grid. Twenty fields were evaluated for each patient. A random selection of the fields was located as described on points of a lattice grid. Twenty fields were evaluated for each patient. A random selection of the fields was located as described [8].

Statistical analysis

Because of the small number of patients in each group, non-parametric statistical methods were used. Probability values less than 0.05 were considered statistically significant. Results are expressed as the mean ± standard deviation. The Wilcoxon test was used to make group comparisons for continuous variables. Comparisons between the two groups were made with the Mann-Whitney U test. The histological examination was studied by the pathologist who was blinded to the therapy.

Results

The groups were similar with respect to age, sex, atrial fibrillation, double or single valve replacement and previous operations (Table 1). The preoperative NYHA classes were also similar (all patients were NYHA class III). The operation time, bypass time, cross-clamp time and concomitant surgical procedures were again similar (Table 2). After CPB, the PTX group required a maximum dobutamine dose of 4.7 mcg/kg per min, and the control group required 4.4 mcg/kg per min. The PTX group required a maximum dose of dopamine – 3.3 mcg/kg per min, and the control group required a maximum dose of 3.2 mcg/kg per min. There was no statistical difference between the two groups regarding the dobutamine and the dopamine doses. All the patients had an uncomplicated postoperative recovery, all being weaned from mechanical ventilation and extubated within 26 h. There were no differences between the two groups’ extubation times (PTX mean 11.1±2.6013 h and CT mean 10.9±5.3635 h). The 1st postoperative day blood losses from the mediastinal drains were also similar (PTX mean 382±284 cc, CT mean 370±231 cc). Blood transfusions were required up to 2 h postoperatively in both groups (PTX group required 1.8 unit, CT group required 1.6 unit).

In both groups, the leukocyte count (CTA 6.97±1.06×10⁹/mm³ and PTXₐ 7.32±1.46×10⁹/mm³) increased 15 min after the cessation of CPB (CTB 12.94±2.57×10⁹/mm³, PTXB 12.08±4.77×10⁹/mm³) and remained high 2 h after the operation (CTC 12.94±3.57×10⁹/mm³ and PTXC 11.53±6.01×10⁹/mm³) but the increase was similar in the two groups. A significant decrease in the platelet count was found in both PTX and CT groups after cessation of CPB, as compared with the respective baseline value (CTₐ 212±50×10³/mm³ to CTC 271±49×10³/mm³ and PTXₐ 205±52×10³/mm³ to PTXC 212±60×10³/mm³) (P<0.05) (Fig. 1). Mean pulmonary arterial pressures were observed to decrease to some extent after CPB (CTₐ 27.2±7.8 mmHg to CTₐ 23.5±4.0 mmHg and PTXₐ 24.5±5.0 mmHg to PTXₐ 22.7±3.5 mmHg) and in the early postoperative period in both groups (CTₐ 23.1±7.3 mmHg and PXₐ 20.5±4.4 mmHg) (Table 3). However, this decrease was not considered statistically significant. Pulmonary capillary wedge pressure dropped considerably after CPB and remained high 2 h after the operation (CTₐ 110±50×10³/mm³ and PTXₐ 128±60×10³/mm³) (P<0.05) (Fig. 1).

Pulmonary vascular resistance was similar in both CT and PTX groups before bypass (CTₐ 136±44 and PTXₐ 151±82 dynes·sec·cm⁻², respectively). After cessation of
CPB, a mild increase was observed in both groups (CT_B 177±94 and PTX_B 182±43 dynes·sec·cm⁻⁵), but there was no statistically important difference between the two. The increase of the postoperative PVR in the control group was statistically greater than that of the PTX group (CT_c 219±98 and PTX_c 193±51 dynes·sec·cm⁻⁵), (P<0.05) (Fig. 2).

The mean alveolar-arterial P_O₂ gradient (CT_A 56±14 mmHg and PTX_A 50±20 mmHg) increased significantly (P<0.01) in both PTX and CT groups after cessation of CPB (CT_B 143±42 mmHg and PTX_B 165±27 mmHg) but decreased a little 2 h postoperatively in both groups (CT_c 127±36 mmHg and PTX_c 124±40 mmHg). There were no significant differences between the two groups.

While the number of leukocytes in the CT group found in the lung parenchyma per lattice square area was some 3.60±1.52 before the CPB, it was about 8.86±4.82 following the CPB (Fig. 3A, B). In the PTX group, the value was found to be 4.78±3.02 initially; and 5.58±3.39 after the bypass (Fig. 3C, D). When we compared the increase in the two groups, a considerable difference was seen (P<0.005).

**Discussion**

Contact of blood with synthetic surfaces during CPB results in a systemic inflammatory reaction that includes activation of multiple humoral and cellular mediators of inflammation. Several studies have demonstrated activation of the coagulation cascade, the kallikrein system, the fibrinolytic system, and the complement system [22, 24]. Leukocytes and platelets are the most important components of cellular response during CPB. Leukocyte activation occurs and platelet function is impaired. These humoral and cellular systemic responses are manifest in cardiac surgical practice as the "postperfusion" syndrome with leukocytosis, increased capillary permeability, accumulation.
Fig. 3  A A low neutrophil leukocyte count in the alveolar wall (arrow) before CPB in CT group (Hematoxylin and eosin, original magnification ×272). B Increased neutrophils are noted in the alveolar wall after CPB in CT group (Hematoxylin and eosin, original magnification ×272). C Low numbers of neutrophils in the PTX group before CPB (Hematoxylin and eosin, original magnification ×272). D A similar number of neutrophil leukocytes is noted in the PTX group after CPB (Hematoxylin and eosin, original magnification ×272).

of interstitial fluid, and organ dysfunction [9, 23]. The lung is one of the organs most affected by CPB. Impaired oxygen transport may be a major problem after open heart surgery and can sometimes lead to prolonged intubation in the presence of satisfactory myocardial function. Much recent work has focused on the role of the neutrophil post-bypass pulmonary injury. Neutrophil activation during CPB includes release of neutrophil proteolytic enzymes [31], changes in neutrophil adhesiveness [15], and neutrophil sequestration in the pulmonary vascular bed after re-establishment of pulmonary blood flow [8, 15, 33]. There is a marked increase in the number of polymorphonuclear cells in the pulmonary arterioles and capillaries with CPB [35]. Asada and Xamaguchi noted disintegrated intravascular polymorphonuclear cells in the capillary lumen [3] and Ratliff et al. found no severe endothelial damage in the absence of large numbers of polymorphonuclear leukocytes [30].

Many classic drugs such as steroids [37], protease inhibitors [5], and free radical scavengers [26] have been used in an attempt to reduce the organ damage produced by CPB. Both corticosteroids [38] and aprotinin [39] reduce plasma levels of neutrophil elastase after aortic cross-clamp removal, and dexamethasone administration prevents tumor necrosis factor-α (TNF) production during CPB [21]. Corticosteroids are not used routinely as prophylaxis during CPB; there is no evidence of effective in vivo complement activation, cellular host defense mechanisms are impaired, and higher endotoxin levels have been reported in treated patients [1]. Although some effects of aprotinin on neutrophil elastase were found, the most striking observation was that the operative field was unusually bloodless both during and after the operation [39].

Recent insight into the mechanism of neutrophil adhesion and endothelial injury suggests new strategies for ma-
Manipulating the neutrophil. It is well established that neutrophil adherence to endothelium is a crucial step both in neutrophil-mediated endothelial injury and in the emigration of neutrophils from the vascular to the extravascular space [18, 32]. Experiments to inhibit leukocyte aggregation and sequestration in the lung have used the following agents: DN-9693, a new phosphodiesterase inhibitor [28]; anisodamine, an anticholinergic agent [14]; and monoclonal antibody to CD 18, which prevents neutrophil adhesion to endothelium [11]. No clinical reports with any of the agents have appeared.

Pentoxifylline [3,7-dimethyl-1-(5-oxohexyl)-xanthine] has been shown to have significant hemorrhologic activity: it increases red blood cell flexibility, reduces blood viscosity and filterability, and increases capillary flow in several pathologic states. It has been most widely used for the therapy of patients with various types of vascular insufficiency, especially intermittent claudication. The exact mechanism of these effects is unknown, but they are thought to be related to changes in erythrocyte membrane fluidity. Recently PTX has been shown to decrease polymorphonuclear and mononuclear leukocyte aggregation, adhesion characteristics and filtration resistance [34]. Pentoxifylline decreases superoxide anion production and lysozyme release by polymorphonuclears and macrophages [4]. Additionally, recent interest in the role of endotoxin and the systemic inflammatory cytokines that are thought to play an essential role in the pathogenesis of shock and multiple organ dysfunction during sepsis. Cardiopulmonary bypass may release systemic inflammatory cytokines including tumor necrosis factor (TNF), interleukin-1, and interleukin-6 (IL-6) [6]. Deng et al. also found a temporary increase in IL-6 and TNF within 24 h after CPB [10]. Pentoxifylline inhibits the inflammatory action of IL-1 and TNF on neutrophil function [36, 41]. Models simulating adult respiratory distress syndrome demonstrate a diminution of lung injury if pretreated with PTX [13, 40]. Pentoxifylline reduces neutrophil oxidant production and neutrophil-dependent lung injury [25].

Although hemodynamic changes have been reported following the PTX infusion [19], we did not find any such changes. This may be due to the fact that the patients had been given the drug orally preoperatively.

Cardiac operations and CPB provide a potent stimulus for platelet activation by exposing the blood to the synthetic surfaces of the bypass circuit, to the blood-gas interfaces or to injured endothelial surfaces [12, 17]. In both groups the number of platelets was found to decrease significantly after CPB. However, following CPB this decrease continued in the CT group postoperatively, while a moderate increase was observed in the PTX group. This may be attributed to the ability of the PTX to protect the integrity of platelets due to its anti-aggregate effects [27]. However, postoperative drainage was not found to be different in the two groups.

Although the PVR in both groups was high at the end of CPB, it was still increasing in the CT group 2 h postoperatively. This increase was insignificant in the PTX group. This may be due to the inflammatory response as exhibited by leukocyte sequestration in the lungs. Butler et al. studied the protective effects of PTX on CPB [7]. However, in that study, no leukocyte sequestration was seen in the lungs because CPB was only used for a short time. Therefore, Chenoweth et al. demonstrated a statistically significant positive correlation between the degree of pulmonary sequestration of neutrophils, the duration of CPB and aortic cross-clamping [9]. We found significantly less leukocyte sequestration in the lungs in patients given PTX. The precise mechanism by which PTX attenuated the CPB-induced leukocyte sequestration is unknown, but may be due to a direct effect on the pulmonary endothelial cells, or to an exchange of the physical characteristics of the leukocyte-endothelial cell interaction.

Although the leukocyte sequestration was less in the PTX than the CT group after CPB, the alveolar-arterial P_o2 gradient was not different in the two groups. This probably did not cause any functional changes in the cellular levels, as the preoperative pulmonary function tests of the patients in the study were normal. If pulmonary insufficiency does not develop after CPB, post-pump lung is thought to be caused by pulmonary congestion rather than leukocytic effects. Post-pump lung is seen early after CPB and only lasts a short time. Electron microscopic studies after CPB showed edema in the lung epithelial cells and damage in the mitochondrias [2]. Consequently, in order to evaluate the beneficial effect of PTX in the lung after CPB, we should study more patients who are more likely to suffer from postoperative pulmonary insufficiency and whose pulmonary functions are critical.
References