Pulmonary function after biventricular bypass for autologous lung oxygenation

Nikolaus Mendler*, Werner Heimisch, Hubert Schad

German Heart Center Munich, Department of Cardiac Surgery, Lazarettstrasse 36, D-80636 Munich, Germany

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Abstract

Objective: Biventricular bypass (BVB) with autologous lung perfusion is an attractive concept to ameliorate systemic inflammatory response by eliminating the oxygenator from the extracorporeal circulation. The effect of biventricular bypass as compared to heart-lung bypass (HLB) on pulmonary function parameters was therefore studied in an experimental model.

Methods: Heart-lung bypass using a membrane oxygenator or biventricular bypass using the autologous lung for gas exchange was performed for 120 min in an alternating series of 12 mongrel dogs with the heart arrested for 90 min by crystalloid cardioplegia and 30 min reperfusion, followed by a 120 min observation period. Systemic (CO, SVR) and pulmonary hemodynamics (PVR), extravascular lung water (EVLW, double indicator), gas exchange (FiO2, PaO2, PaCO2), lung compliance (PC), and ventilation (RMV) at FiO2 ≈ 0.5 required to maintain PaCO2 at 40 mmHg, were measured. Blood cell counts (Leuco, Thrombo) were performed.

Results: All animals were weaned from extracorporeal circulation without inotropes, no differences were observed in cardiac output and blood pressures. The following data were obtained in % change from pre-bypass values 60 min after extracorporeal circulation (*: P < 0.05, HLB vs. BVB): PVR, 1108 vs. 145*; EVLW, 121 vs. 22*; PC, 1212 vs. 14*; PaO2, 121 vs. 121; RMV, 121 vs. 12*; Leuco, -65 vs. -12*; Thrombo, -62 vs. -35*. Conclusion: During and after heart-lung bypass the lung is subject to severe ischemia-reperfusion injury as indicated by edema, cell trapping, and impaired gas exchange. The data demonstrate superior preservation of pulmonary mechanics and function after biventricular bypass as compared to heart-lung bypass and support the clinical strategy of using biventricular bypass in patients with impaired lung function. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Extracorporeal circulation; Heart-lung bypass; Biventricular bypass; Pulmonary edema; Lung function

1. Introduction

The technique of biventricular heart bypass (BVB) using the patient’s own lungs for gaseous exchange was established by Charles Drew in the late 1950s as a routine procedure for the correction of congenital cardiac malformations during cardiocirculatory arrest in profound hypothermia [1,2]. This development was prompted by the devastating biocompatibility of the oxygenators in these days with their large blood-gas interface [3]. The advent of present-day membrane oxygenators has ameliorated many of the early problems described as the post-perfusion syndrome [4,5], but it is still contended that reduction of foreign surface in contact with blood would result in even less noxious extracorporeal circuits. Hence, the technique of Drew has been periodically revived for closed-heart procedures like uncomplicated coronary surgery where air embolism is not a threat [6]. Significant biochemical and clinical benefit using BVB was shown for complement activation [7] and systemic inflammatory response [8] as compared to standard cardiopulmonary bypass. The lung and formed elements of blood are specifically on target from these perioperative noxes, and pulmonary functional and biomechanical parameters together with leucocyte and platelet counts were therefore assessed in an experimental model comparing biventricular bypass using autologous lung perfusion to cardiopulmonary bypass using a membrane oxygenator.

2. Methods

2.1. Animals and anesthesia

The experiments were performed in 12 mongrel dogs of both sexes with body weight 23.3 ± 0.6 kg. The animals were pretreated with a phenothiazine derivative (1 mg/kg Combelen® i.m., Bayer, Leverkusen, FRG). Anaesthesia was induced by pentobarbital (12 mg/kg Nembutal® i.v.,
Abbott, Wiesbaden, FRG) and maintained by infusion of piritramide (0.6 mg /kg per h Dipidolor®, Janssen, Neuss, FRG). The animals were paralyzed by infusion of pancuronium (Organon, Eppelheim, FRG) 0.1 mg/kg priming, 0.1 mg/kg per h sustaining dose and artificially ventilated (f = 15/min) via an endotracheal tube with O₂:NO2 = 1:1 at a tidal volume (V₉ = 12–15 ml/kg) appropriate to maintain arterial pCO₂ at 35–40 mmHg (Servo Ventilator 900, Dräger, Lübeck, FRG).

A positive end-expiratory pressure (PEEP) of 5 cmH₂O was maintained throughout the experiment. NaHCO₃ (1 mol/l) was substituted as necessary to keep the base excess above 3 mmol/l. Plasma K⁺ was kept at 4.5–5.5 mmol/l by i.v. infusion of K-aspartate (Inzolen®, Kölher, Alsbach, FRG) as required. Esophageal and rectal temperatures were monitored by a thermistor probe. Arterial blood gases, base excess, HCT, and K⁺ were checked every 15 min (Corning 168 pH-Bloodgas Analyzer, Corning Medical Inc., Medfield, USA). The electrocardiogram was monitored from standard lead II. The animals received humane care in compliance with the European Convention on Animal Care, the study was approved by the institutional ethics committee and the governmental animal protection supervising body.

2.2. Preparation and instrumentation

The left external jugular vein and the right femoral artery were cannulated for application of drugs and fluids, blood sampling, and monitoring of aortic (AoP) and right atrial (RaP) blood pressures by fluid-filled manometers (P23 Db, Statham, Oxnard, CA). Respiratory pressure inside the endotracheal tube was continuously recorded by the same technique. The heart was exposed from the fifth left intercostal space and suspended in a pericardial cradle. An electromagnetic flow probe (SP-2202, Statham, Oxnard, CA) was placed around the ascending aorta to measure cardiac output (CO). Catheters were placed into the main pulmonary artery for pressure recording and into the ascending aorta for blood withdrawal.

Extravascular lung water (EVLW) was determined by the thermal-dye indicator method [9] in duplicate measurements. An iced dye bolus (0.025 mg/kg Cardio-Green, Hynson and Ass., Baltimore, MD) was flushed into the right atrium, blood was withdrawn from the aortic arch at 40 ml/min through a densitometer (Fa. Brechtelsbauer, Munich) cuvette. Temperature was recorded from the catheter tip. Thermal and dye dilution curves were analog recorded and corrected for appearance time. After digitizing by a desk-top computer (HP-8945B, Hewlet Packard, Böblingen, FRG) monoexponential decays were extrapolated over three decades and mean transit times (MTT) were computed for calculation of EVLW = CO × (MTTthreo – MTTbry). Aspirated blood was immediately returned to the animal.

Pulmonary vascular resistance before and after BVB was calculated from \( PVR = \frac{PAP}{CO} \). On BVB, pump flow was substituted for CO. For computation of pulmonary compliance (PC) tidal volume as read from the respirator was divided by inspiratory plateau pressure at a constant PEEP of 5 cmH₂O which was maintained throughout the experiment.

For each measurement of PC tidal volume was varied in five steps over a 1 min period and PC was calculated from the slope of the volume/pressure curve: \( PC = \frac{dV}{dP} \).

After heparinization (500 U/kg, Liquemin®, Roche, Grenzach, FRG) cannulae were placed into the aortic arch (6 mm) and the right atrium (32 F Stöckert, Munich, FRG) for cardiopulmonary bypass. For biventricular bypass the same cannulation was performed in the main pulmonary artery and the left atrium. A left ventricular vent (12 F) was advanced from the left atrial appendage. After connection of all lines to the extracorporeal circuit perfusion commenced after a 15 min control period.

2.3. Experimental protocol

In both groups 1000 ml of Ringer’s lactate with 20 mmol bicarbonate was used to prime the circuit. After initiation of bypass at a flow of 100 ml/kg per min and during cooling to 30–28°C the heart was fibrillated, the aorta cross-clamped and 500 ml ice-cold crystalloid cardioplegic solution (Bretschneider HTK, Kölher, Alsbach, FRG) were infused by gravity into the aortic root. Ischemia was maintained for 90 min, followed by a 30 min reperfusion period with rewarming. After 120 min, bypass was discontinued without the use of inotropes. Decannulation was followed by a 2 h observation period. No pericardial blood was returned to the circuit. After BVB and HLB ventilation was adjusted as required to maintain PaCO₂ at 40 mmHg. FiO₂ was increased from 0.5 to 1.0 at 15 and 120 min post bypass for 5 min periods for determination of maximal attainable PaO₂.

2.4. Heart-lung bypass (HLB)

The circuit consisted of a pediatric hollow fiber membrane oxygenator (Masterflow 702, Dideco, Mirandola, Italy) with integral heat exchanger and a collapsible bag reservoir using a roller pump (Weishaar-Elektronik, München, FRG) and silastic tubing.

2.5. Biventricular bypass (BVB)

The circuit was made up from two collapsible bag reservoirs, interconnected by a shunt line. This was closed during going on and off bypass first on the right side. Once rated flow was established, the two roller pumps were synchronized so that a small left to right shunt persisted to avoid venous admixture to the arterial system. A disposable heat exchanger (D-720 P, Dideco, Mirandola, Italy) was included in the arterial line.
2.6. Data analysis and statistics

Hemodynamic and ventilation variables, temperature, and heart rate were continuously monitored on a multi-channel recorder (Brush 481, Gould, Cleveland, OH) for analysis. All data were evaluated at end-expiration. Data are given as mean ± SEM or in % of pre-bypass values ± SEM, respectively. Statistical evaluation was performed by the Wilcoxon matched pair signed rank test for longitudinal differences within one group and by Student’s t-test for intergroup differences, at a level \( P < 0.05 \).

3. Results

The conduct of perfusion, initiation of cardioplegia, cooling and rewarming, reperfusion, and weaning from bypass was equally easy to manage using both extra-corporeal circulation techniques. No inotropes or vasopressors were needed to re-establish adequate circulation. In BVB, effective venting of the left ventricle was found important to prevent washout of cardioplegia by arterialized blood from the left atrium with consequent resumption of myocardial activity. This occurred in 2/6 animals and was easily managed by repositioning of the vent and a second dose of cardioplegia.

3.1. Central hemodynamics

Hemodilution was not different in both groups, resulting in a drop of HCT from 36 ± 2 to 21 ± 2 in HLB and from 37 ± 3 to 24 ± 2 in BVB after initiation of perfusion, returning to 27 ± 2 in both groups 2 h after termination of bypass. Mean arterial blood pressure during the control period was 105 ± 7 mmHg in HLB and 98 ± 8 mmHg in BVB animals and dropped steadily during perfusion to 72 ± 3 on HLB and 70 ± 2 mmHg on BVB, recovering to 84 ± 4 mmHg 2 h after HLB and to 80 ± 3 mmHg after BVB. Initial cardiac output was 2.4 ± 0.2 l/min before HLB and 2.6 ± 0.3 l/min before BVB and reached 90% of control in both groups 2 h after perfusion. Total peripheral resistance was equal (41 mmHg/l per min) before perfusion and at the end of the observation period (37 mmHg/l per min). At no time during the experiments significant group differences were observed in the above parameters.

Pulmonary vascular resistance (Fig. 1) did not change from 7 mmHg/l per min during the control period in both groups. On BVB a drop in PAP from 15 ± 2.5 to 12 ± 3 mmHg was observed at the rated bypass flow of 100 ml/kg per min which remained stable throughout the entire period of autologous extracorporeal lung perfusion. Fifteen minutes after termination of bypass PVR was reduced to 85% of the control value in both groups, showing an increase after 1 h to 121% in the HLB group which was significantly higher as compared to BVB (108%), and returning to control level in both groups towards the end of the experiment.

3.2. Lung mechanics

Pulmonary compliance did not differ during the control period (66 ± 7 ml/mmHg before HLB vs. 58 ± 8 ml/mmHg before BVB). However, it was increased after BVB and decreased after HLB at all observation points after extra-corporeal circulation (Fig. 1), with a maximal group difference of 16% early after bypass. Extravascular lung water was similar in both groups before perfusion (6.6 ± 0.4 ml/kg before HLB vs. 7.1 ± 0.5 ml/kg before BVB). It did not change after weaning from BVB but was significantly increased throughout the post-bypass observation period after HLB, reaching 133% of control at the end of the experiment (Fig. 1).

3.3. Gas exchange

No significant difference was observed between groups in
arterial oxygen tension, which was stable throughout the aortic crossclamp time of 90 min, and showing a parallel drop during myocardial reperfusion and rewarming (Fig. 2). When FiO₂ was increased from 0.5 to 1.0 before and 15 and 120 after bypass, PaO₂ was elevated equally by approx. 200 mmHg in both groups.

Respiratory minute volume as adjusted to maintain normoventilation (Fig. 2) did not differ between HLB and BVB animals before bypass. RMV was continued at this level (320 ± 20 ml/kg per min) throughout BVB. On HLB, lungs were arrested and inflated with 50% O₂/N₂O at 5 cmH₂O pressure. During bypass in hypothermia (30–28°C) hypocapnia was observed in both groups which was generally more pronounced in HLB (Fig. 2).

After weaning from extracorporeal circulation ventilation was again adjusted to a target value of 40 mmHg for PaCO₂. This was achieved in both groups (Fig. 2). However, a significantly higher RMV reaching up to 400 ml/kg per min was needed after HLB, whereas the preoperative RMV could be maintained after BVB.

3.4. Blood cell counts

The time course for leucocyte and thrombocyte count is shown in Fig. 3. Equally reduced by hemodilution in both groups, counts recovered on bypass, but more so in the BVB group. At the end of bypass the difference became significant during the myocardial reperfusion and rewarming phase. After termination of ECC a drop of cell counts was observed in both groups which was more pronounced after HLB and did not reverse during 120 min post-bypass. In contrast, leucocytes and thrombocytes were significantly better preserved after BVB with a marked tendency to recover during the observation period, where leucocytes counts reached pre-bypass values and thrombocytes 75% thereof. At the same time, cell counts remained depressed to 40% of control after HLB.

4. Discussion

In the present experiments no difference was apparent in the hemodynamic reaction to 2 h extracorporeal circulation including a 90 min period of cardioplegia when either HLB
or BVB was used and the animals were observed for 2 h thereafter. While myocardial performance and circulatory response were not differently affected, pulmonary biophysical and gas transfer parameters showed a markedly deviating reaction, highlighted in extravasation of fluid in the lungs, increased mechanical stiffness, and impaired diffusion capacity when HLB and an oxygenator were used.

The artificial surface of the oxygenator provides a massive stimulus for activation of coagulation and even high doses of heparin fail to completely inhibit thrombin generation which activates platelets and leucocytes and stimulates the endothelium to release inflammatory mediators [10,11]. Also, HLB triggers the complement cascade, ultimately activating the terminal complement complex, neutrophils, elastase, and the proinflammatory cytokines [12,13]. During HLB with exclusion of the lungs from the circulation blood stasis in the pulmonary vasculature contributes to endothelial dysfunction resulting in a highly vulnerable microcirculation upon reperfusion [14]. Sequestration of neutrophils in the lung after HLB has been demonstrated [15], associated with an increase in plasma levels of humoral mediators of inflammation [16], in particular C3a and C5a, and accompanied by release of proteolytic enzymes from neutrophil granules and generation of toxic oxygen radicals [17]. The common result of these effects is endothelial cell swelling, fluid, and lymphocyte extravasation, and consequently, increased vascular resistance, and impaired diffusion [18,19]. The results of the present study are in agreement with this pathophysiological concept and also with the findings on complement activation by Glenville and Ross [7] and Tassani et al. [8] comparing HLB and BVB in a clinical study.

The time course of the inflammatory response was probably not well accounted for in the experimental protocol of this study, limiting the observation time to 2 h after bypass. The evolutions of pulmonary edema, impaired CO2 elimination and leucocyte depletion appear to persist beyond this period (Figs. 2 and 3). Clinical studies indicate that transcription of inflammatory mediators, in particular IL6, takes time [20] and highest levels of IL6 were found 4 h after HLB in a recent study [8]. In addition, test systems for determination of inflammatory mediators in the dog model were not available at the time of the experiments. Ongoing augmentation of the differences observed in this experimental study might be expected if the chest of the animals had been closed in a clinical time frame. Mechanical restriction of the space available to the edematous lungs would then further aggravate the resistance to pulmonary circulation by increased transmural pressure.

The benefit of using BVB may be dual. For one, elimination of the oxygenator reduces foreign material surface area and, hence, contact activation of complement and inflammatory mediators and also reduces trapping of formed blood elements in the extracorporeal circulation as indicated by the differential time course of cell counts during perfusion. Secondly, uninterrupted flow through the lungs avoids stasis and, hence, reperfusion injury. Surgical limitations of the technique are obvious: It is necessary to place four cannulae in the operating field which may hamper manipulation of the heart without obstructing systemic or pulmonary venous drainage. Also, the technique may not safely be used for procedures where air may enter the heart. Conversely, prolonged circulatory assist on either side of the heart is easily maintained when coming off bypass is difficult.

The result of this experimental study have confirmed previous observations and prompted a prospective randomized clinical trial using biventricular bypass for coronary artery revascularization [21] with emphasis on systemic inflammatory response and clinical outcome.

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References


Appendix A. Conference discussion

**Dr Z. Al Halees (Riyadh, Saudi Arabia):** What is the ventilation protocol for the biventricular bypass?

**Dr Mendler:** We first thought that during bypass in moderate hypothermia we might reduce the respiratory minute volume. Surprisingly, this was not the case. Therefore, we ventilated the animals at a rate of 15/min and a respiratory minute volume of approximately 300ml/kg/min throughout the perfusion.

**Dr Al Halees:** And the group that were a regular heart-lung bypass, were they ventilated?

**Dr Mendler:** The lungs were arrested under gentle inflation with air at a positive pressure of 5 cmH2O.

**Dr Al Halees:** Have you tried a group where you had a similar ventilation protocol with the heart-lung bypass and see if there was any difference?

**Dr Mendler:** No, we did not ventilate the lungs in animals on heart-lung bypass.

**Dr C. Mullangi (Dallas, TX):** We did some labs using a calf model in Dallas, Texas, when we did only right heart support, perfusing from 2 to 4 h.

I did lung biopsies on a series of animals, and one striking thing I found was there is very little perivascular infiltration, much less than what we see with the normal conventional bypass. It is quite understandable with your technique there will be less lung damage, so have you had any experience on lung biopsies and tissue edema in the lungs?

**Dr Mendler:** All lungs were fixed in formalin and examined by a pathologist who is a know expert in the adult respiratory distress syndrome. All samples were blinded. After histologic examination he was 100% right in assigning the specimens to the experimental group, mainly based on inflammatory reactions, leukocyte extravasation, and sign typical of reperfusion injury in the HLB group. Unfortunately, I have this only by oral communication and I was unable to obtain a documentation in writing.

**Dr O.H. Frazier (Houston, TX):** How many cases have you done like this?

**Dr Mendler:** There are about 50 patients now.

**Dr Frazier:** That’s very interesting. We had 64 like this in the early ‘90s, and with high-risk cases I do think it has a role. We need to look at it again.

**Dr Mendler:** I am aware of one clinical study published in Lancet by Glenville and Ross in 1986, and they had also about 30 patients and were very happy with their technique. I wonder if they did go on with this procedure.