Biomarkers of Lung Injury in Cardiothoracic Surgery

Engels, Gerwin

CHAPTER 4

The effect of pulsatile cardiopulmonary bypass on lung function in elderly patients

Gerwin Engels, Mikhail Dodonov, Gerhard Rakhorst, Willem van Oeveren, Aldo Milano, YJ Gu and Giuseppe Faggian

International Journal of Artificial Organs. 2014;37(9):679-87.

Abstract

Cardiopulmonary bypass is still a major cause of lung injury and delay in pulmonary recovery after cardiac surgery. Although it has been shown that pulsatile flow induced by intra-aortic balloon pumping is beneficial for preserving lung function, it is not clear if the same beneficial effect can be accomplished with pulsatile flow generated in the extracorporeal circuit. Therefore, we investigated the effect of pulsatile flow, produced by a centrifugal pump, on lung function in elderly patients.

Serial measurements of lung biomarkers Clara cell 16 kD protein, surfactant protein D, and elastase were performed on blood samples from 37 elderly patients (≥75 years) who underwent elective aortic valve replacement surgery with CPB, either with pulsatile perfusion or continuous perfusion. Pulmonary function was assessed by postoperative ventilation time, the arterial blood oxygenation (PaO_2/FiO_2), the alveolar-arterial oxygen gradient (Aa-O_2 gradient) and the pulmonary vascular resistance indexed by body surface area (PVRi).

There was no difference in lung function between both groups, as assessed by the postoperative ventilation time, the PaO_2/FiO_2 ratio, and the Aa-O_2 gradient. The PVRi, however, was significantly lower in the pulsatile perfusion group 15 min after the administration of protamine ($p<0.05$). The plasma concentrations of the lung biomarkers increased during surgery and peaked at 2 h ICU, there were however no differences between groups.

Pulsatile flow does not seem beneficial to postoperative lung function in elderly patients. Moreover, pulsatile flow does not affect lung function on a subclinical level as assessed by lung biomarkers.

Introduction

Cardiopulmonary bypass (CPB) is still a major cause of lung injury and delay in pulmonary recovery after cardiac surgery [1, 2]. This manifests in the form of hypoxemia to acute respiratory distress syndrome.

The use of pulsatile flow in CPB is a topic under much controversy, with reports being in favor of the technique [3] and others which do not find any benefit [4]. The reasoning in favor of pulsatile flow is that mimicking the physiological situation as much as possible will give a better outcome. In more detail, the extra amount of energy induced by pulsatile flow (surplus hemodynamic energy, SHE), should yield better perfusion of the (peripheral) capillaries by means of enhanced microvascular flow.

During CPB, the perfusion of the lungs is limited to the bronchial circulation, and, in fact, this bronchial circulation is strongly reduced [5]. This reduction of the bronchial circulation could add to the ischemic injury of the lungs. Moreover, it has been shown that ligation of the bronchial artery clearly worsens lung function after CPB [6], indicating the importance of bronchial circulation in preventing or attenuating ischemia/reperfusion (I/R) injury. Pulsatile flow is potentially beneficial for perfusion of the lungs via the bronchial arteries. It has been shown that pulsatile flow, induced by means of intra-aortic balloon pumping, preserved lung function in patients with chronic obstructive pulmonary disease (COPD) [7] and in elderly patients [8]. More recently, pulsatile pulmonary perfusion reduced pulmonary hemodynamic parameters and respiratory indices in low-risk CABG patients [9], indicating the beneficial effect of pulsatile flow.

With increasing life expectancies and the use of percutaneous coronary angioplasty, patients are getting older before needing cardiac surgery. These patients run a higher risk for morbidity and mortality after cardiac surgery [10], and potentially benefit more from the use of pulsatile flow.

Although it has been shown that pulsatile flow induced by intra-aortic balloon pumping is beneficial for preserving lung function [7], it is not clear if the same beneficial effect can be accomplished with pulsatile flow generated in the extracorporeal circuit. Therefore, we investigated the effect of pulsatile flow, produced by a centrifugal pump, on lung function in elderly patients. Lung function was evaluated by duration of postoperative ventilatory support, the arterial blood oxygenation (PaO_2/FiO_2), the alveolar-arterial oxygen gradient (Aa-O_2 gradient), and the pulmonary vascular resistance indexed by body surface area (PVRi). Finally, biochemical markers of lung injury were determined.

Materials and Methods

Patients

Elderly patients (≥75 years) undergoing aortic valve replacement surgery with cardiopulmonary bypass in the University Hospital of Verona were prospectively included in this study. Patients with indications for concomitant one-vessel CABG or those with concomitant non-critical coronary artery disease (CAD) were included. The exclusion criteria were: indications for other associated heart procedures, myocardial infarction within the previous month, insulin-dependent diabetes, renal insufficiency with preoperative creatinine level >200 mmol/l, history of systemic inflammatory disease, ongoing corticosteroid therapy, previous radiotherapy or chemotherapy, emergency procedures, patients in inotropic support, IABP or circulatory assistance and re-operations. The study protocol was approved by the local institutional review board, and all patients gave informed consent.

Study groups and interventions

Patients were randomly allocated to a pulsatile perfusion group (Pulsatile, n = 18) or a non-pulsatile perfusion group (Control, n = 19). Pulsatile flow was generated by means of a Deltastream DP3 pump (Medos Medizintechnik, Stolberg, Germany) in the pulsatile operation modus. The pump speed ranged between 3500 rpm and 8500 rpm and the pulse frequency was set to 60 beats per minute. In the control group the pump was set to continuous flow.

All other components of the CPB circuit were the same between groups and were carefully selected according to their capacity to provide the maximum pulse delivery to the patient. The circuit consisted of a Maquet Quadrox-i Adult hollow fiber Softline®-coated membrane oxygenator with integrated heat exchanger, a Maquet Jostra Quart external screen-type arterial filter (pore size 40 μm), a corresponding Softline®-coated tubing system with constant arterial line length from oxygenator to the aortic cannula of 145 + 10 cm, and an Edwards 20.3 cm aortic cannula with vented 3/8" connection site (Luer Lock), 22-24 FR.

According to the model of Shepard *et al* [11], the energy equivalent pressure (EEP) and the surplus hemodynamic energy (SHE) were estimated. In brief, EEP was calculated with the following equation:

$$EEP = \frac{\int f p dt}{\int f dt} \tag{4.1}$$

where f is the pump flow (mL/min) and p is the arterial pressure (mmHg). The SHE (ergs/cm^3) was calculated by the following equation:

$$SHE = 1332\left[\frac{\int fpdt}{\int fdt} - MAP\right] \tag{4.2}$$

The difference between the EEP and the mean arterial pressure (MAP) is the extra energy generated by the pulsatile device and is approximately 10% in the normal physiological situation [12].

For precise EEP calculation, flow curves obtained from external flow sensors (Transonic HT-110; Transonic Systems, Ithaca, NY, USA) and pressure curves obtained from pressure transducers were recorded simultaneously at pump outflow, post-oxygenator, aortic cannula level, and the radial artery.

Anesthesia and surgery

Anesthesia was provided according to a standardized protocol. Premedication consisted of oral diazepam two hours before surgery. General anesthesia was induced with propofol and sufentanil.

Ventilatory management was aimed at an inspiratory oxygen fraction of 0.5,a positive end-expiratory pressure of 6 cm H_2O, and a tidal volume of 6 ml/kg to 8 ml/kg. The central venous catheter and a Swan-Ganz catheter (Arrow International, Reading, PA, USA) were inserted in the right internal jugular or right subclavian vein and an indwelling bladder catheter for urine collection was routinely utilized. After anesthesia induction the patients received 2.0 g of cefuroxim (or 600 mg of clindamycine when allergic to penicillin). Anesthesia was maintained with propofol infusion and boluses of sufentanil and vecuronium. Transfusion of packed red blood cells (RBC) was indicated at hemoglobin levels <7 g/l during CPB and at hemoglo- bin levels <9 g/l afterwards. An activated clotting time of >480 s was achieved by administration of heparin (4 mg/kg) before starting CPB.

In both groups, the CPB circuit was primed with 1500 mL of balanced saline solution, while the flow was maintained at 2.4 L/min per m^2. The CPB was performed in normothermic conditions with mean arterial pressure (MAP) maintained between 50 mmHg and 80 mmHg. The vent was positioned into the left ventricle through the right superior pulmonary vein and patients were not ventilated during CPB. After finishing CPB, protamine (4 mg/kg) was infused to neutralize the heparin.

Blood samples were taken after induction of anesthesia (Pre-op), at sternal wound closure (Post-op), two hours after arrival at the intensive care unit (2 h ICU) and eighteen hours after arrival in the ICU (Day 1). Upon the start of reperfusion, two additional blood

samples were taken from the vena cava and the pulmonary vein. Plasma was obtained by centrifugation of whole blood at 1100×g for 10 min. Thereafter, plasma was aliquoted and stored at -80°C for later analysis.

Clinical and biochemical measurements

Pulmonary function was assessed by duration of postoperative ventilatory support, the arterial blood oxygenation (PaO_2/FiO_2), the alveolar-arterial oxygen gradient (Aa-O_2 gradient), and the pulmonary vascular resistance indexed by body surface area (PVRi). These measurements were taken at the same time-point as blood samples were taken. The PVRi was measured at two additional time-points; during CPB and just before the administration of protamine (Before prot), and 15 min after the administration of protamine (15' prot).

Elastase plasma concentration, as a marker of leukocyte activation, was determined by means of sandwich ELISA. Antibodies were purchased from Affinity Biologicals (Ancaster, ON, Canada). Elastase isolated from human donor leukocytes (Merck KGaA, Darmstadt, Germany) served as a standard.

Surfactant protein D plasma concentration, as a marker of alveolar capillary membrane integrity, was also measured by means of sandwich ELISA. Capture and detection antibodies were from R&D Systems (Minneapolis, MN, USA). Recombinant human surfactant protein D (also from R&D Systems) served as a standard.

Clara cell 16 kD protein (CC16), a marker of respiratory epithelial integrity originating predominantly from the (terminal) bronchioles, was measured in plasma by means of an in-house developed sandwich ELISA. Recombinant human CC16 (R&D Systems) served as a standard. A monoclonal rat antibody to human CC16 (R&D Systems) was used as capture antibody and monoclonal mouse antibody to human CC16 (Hycult, Uden, The Netherlands) was used as detection antibody.

Data and data analysis

All values are summarized as mean plus standard error of the mean, unless specified otherwise. Student's t-test was used to compare means of continuous variables and when variables where non-normally distributed the Mann-Whitney U test was used. Contingency tables, χ^2, and Fisher exact tests were used as appropriate. A two-way mixed ANOVA was used to compare serial data. Violations of sphericity were Greenhouse-Geisser corrected. Correlations between pulmonary vascular resistance, elastase plasma concentrations, and CC16 plasma concentrations were assessed by Pearson's correlation coefficient. All tests performed in order to test the (null-) hypothesis of no difference

Table 4.1: *Patient demographic data*

Variable	Control (n=19)	Pulsatile (n=18)	p value[a]
Age [years]	79 (3)	80 (3)	0.515
Height [cm]	165 (9)	167 (9)	0.521
Weight [kg]	68 (14)	73 (914)	0.321
Male [No.]	11 (58%)	9 (45%)	0.746
Coexisting illness [No.]			
Diabetes	3 (18%)	6 (33%)	0.443
Pulmonary disease	2 (11%)	2 (11%)	1.000

Data are presented as mean (standard deviation). [a] Student's t-test, Pearson's χ^2 or Fisher exact test used as appropriate.

were two-sided. A p value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

In this study the effect of pulsatile flow on lung injury during cardiopulmonary bypass was evaluated. The average age of the patients was 80 ± 3 years and the mean EuroSCORE was 5.5 ± 1.3. Patient characteristics (Table 4.1) were not significantly different between groups.

In the pulsatile perfusion group, measured at the radial artery, the EEP was 59 ± 11 mmHg (7.0% higher than MAP) and the SHE was 4980 ± 2324 erg/cm^3, while a physiological EEP is approximately 10% higher than MAP [12].

Postoperative results and clinical outcomes

Postoperative variables such as ventilation time, ICU time and hospital stay did not differ between both groups (Table 4.2). There was no difference in lung function between both groups, as assessed by PaO_2/FiO_2 ratio and the Aa-O_2 gradient (Table 4.3). Blood oxygenation (PaO_2/FiO_2) dropped following surgery and was restored again in the ICU, although levels were still lower on the first postoperative day as compared to pre-operative values (Table 4.3). The Aa-O_2 gradient depicted an opposite trend, it increased following surgery after which it returned to baseline values, although still slightly elevated as compared to pre-operative values.

The PVRi differed between time-points (p<0.001) but not between groups or the interaction of group and time, as indicated by two-way mixed ANOVA (Table 4.3). During cardiopulmonary bypass the PVRi decreased, and after protamine administration the

Table 4.2: *Summary of postoperative clinical data and CPB characteristics*

Variable	Control (n=19)	Pulsatile (n=18)	p value[a]
CPB [min]	81 (68-103)	96 (67-105)	0.638
Cross clamp [min]	63 (49-78)	69 (50-81)	0.820
MAP [mmHg]	60.9 (12.6)	54.6 (9.5)	0.096
Flow [L/min]	4.3 (0.5)	4.5 (0.5)	0.200
EEP [mmHg]	60.2 (13.6)	58.5 (10.8)	0.690
EEP-MAP [%]	0	6.97 (3.2)	<0.001
SHE [ergs/cm^3]	0	4980 (2324)	<0.001
ICU time [h]	22 (20-44)	26 (20-52)	0.713
Ventilation time [h]	12 (11-17)	14 (10-18)	0.807
Hospital stay [days]	9 (8-13)	9 (8-10)	0.700

Data are presented as mean (standard deviation) or median (interquartile range) unless stated otherwise. [a] Student's t-test or Mann-Whitney U test used as appropriate.

PVRi increased again, peaking at 2 h ICU, after which it returned to baseline. The control group was significantly higher 15 min after administration of protamine as compared to the pulsatile group (Figure 4.1, $p = 0.013$, Student's t-test).

Lung injury markers

Neutrophil elastase was measured as a marker for leukocyte activation. Elastase differed between time-points (p<0.001), peaking at 2 h ICU, but did not differ between groups or the interaction of both (Table 4.4).

Surfactant protein D increased significantly after surgery (p<0.001), and returned to baseline on the first post-operative morning. There were no significant differences between the groups or the interaction of group and time-points.

For Clara Cell 16 protein an identical trend was observed. CC16 increased following surgery (p<0.001), peaking at 2 h ICU, and returned to baseline on the first post-operative day. Again there was no significant difference between groups.

Trans-pulmonary lung injury marker measurements

Besides perioperative serial measurements, blood samples were drawn from the vena cava (VC) and the pulmonary vein (PV) directly following reperfusion. These samples were used to establish a transpulmonary gradient ($\text{Concentration}_{PV} - \text{Concentration}_{VC}$) of lung injury markers.

Table 4.3: *Pulmonary vascular resistance index, PaO_2/FiO_2 ratio and Aa-O_2 gradient*

Variable	Pre-op	Before protamine	Post-op/ 15' after protamine	2 h ICU	Day 1	p values[a] Groups	Timepoints	Interaction
PaO_2/FiO_2 [mmHg]						0.254	<0.001	0.803
Control	435 (151)	NA	277 (109)	337 (82)	293 (82)			
Pulsatile	393 (268)	NA	233 (111)	292 (92)	275 (100)			
AaO_2 gradient [mmHg]						0.253	<0.001	0.708
Control	103 (81)	NA	173 (56)	133 (55)	135 (46)			
Pulsatile	118 (124)	NA	210 (106)	163 (89)	155 (74)			
PVRi [dyn·s/cm^5/m^2]						0.186	<0.001	0.146
Control	308 (122)	251 (93)	334 (102)	437 (156)	285 (113)			
Pulsatile	306 (117)	229 (88)	235 (121)	334 (153)	306 (118)			

Data are presented as mean (standard deviation). NA = not available. [a] Two-way mixed ANOVA.

Table 4.4: *Concentrations of lung biomarkers in patients perfused with pulsatile flow or continuous flow*

						p values[a]	
Variable	Pre-op	Post-op	2 h ICU	Day 1	Groups	Timepoints	Interaction
Elastase [μg/mL]					0.969	<0.001	0.876
Control	0.97 (0.71-1.50)	13.7 (10.6-16.1)	9.44 (6.85-12.2)	4.03 (2.99-6.27)			
Pulsatile	1.05 (0.90-1.65)	12.9 (10.5-15.6)	8.96 (7.40-11.5)	3.63 (3.12-4.40)			
SP-D [ng/mL]					0.238	<0.001	0.440
Control	34.8 (27.1-63.1)	73.1 (49.1-110)	55.4 (35.1-95.7)	46.6 (25.6-60.8)			
Pulsatile	28.9 (19.5-47.7)	52.5 (35.8-82.5)	50.5 (31.3-76.7)	35.5 (24.0-54.3)			
CC16 [ng/mL]					0.357	<0.001	0.534
Control	29.4 (20.9-47.2)	65.3 (46.7-121)	56.7 (38.3-102)	31.0 (13.5-40.3)			
Pulsatile	21.3 (12.6-28.8)	38.7 (28.2-91.3)	33.3 (24.3-64.1)	25.1 (16.6-58.1)			

Data are presented as median (interquartile range). [a] Two-way mixed ANOVA.

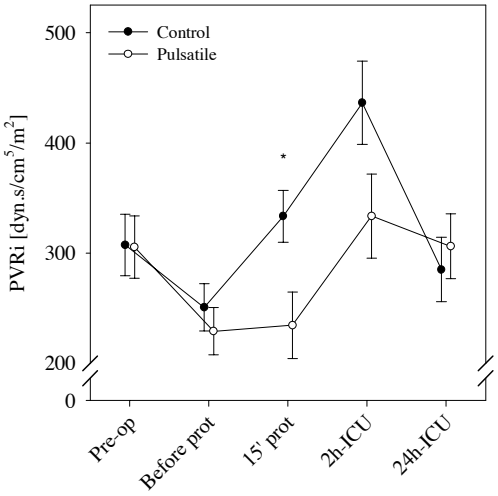

Figure 4.1: *Pulmonary vascular resistance indexed by body surface area in patients perfused with pulsatile flow (open symbols) or continuous flow (closed symbols). * $p < 0.05$.*

The transpulmonary elastase gradient was higher in the control group than in the pulsatile group, 5.04 ± 1.04 and 2.39 ± 1.09 μg/ml, respectively (Figure 4.2A). However, the difference in gradient between groups was not significant ($p = 0.089$).

Surfactant protein D concentrations did not exhibit a gradient (Figure 4.2B). Likewise, there was no difference between both groups ($p = 0.096$).

Clara cell 16 protein was higher in the pulsatile group than in the control group, 18.1 ± 6.8 and 12.2 ± 6.5 ng/ml, respectively (Figure 4.2C). Again, there was no significant difference between groups ($p = 0.535$).

In investigating the relation between PVRi and the biomarkers we found that there was a significant correlation between PVRi before the administration of protamine and the transpulmonary gradient of elastase. Additionally, PVRi before the administration of protamine correlated with the transpulmonary gradient CC16 (Table 4.5).

Discussion

In this study we investigated the effect of pulsatile flow, produced by a centrifugal pump, on lung function in elderly patients undergoing aortic valve replacement surgery. We found that there was no difference in clinical outcome parameters. Only the pulmonary

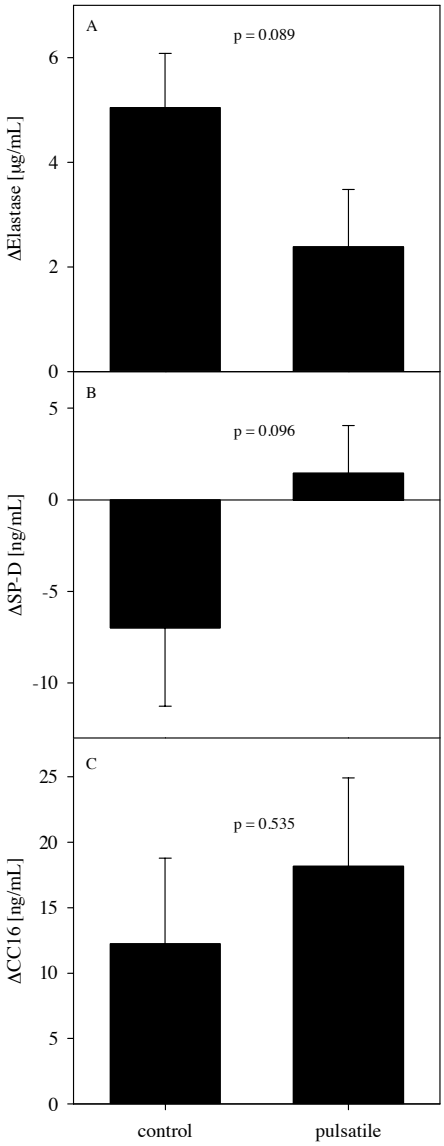

Figure 4.2: *Transpulmonary biomarker gradients. The increase in biomarkers in blood drawn from the vena cava and the pulmonary vein right after the start of reperfusion in patients perfused with pulsatile flow or continuous flow. (**A**) Elastase, (**B**) Surfactant protein D, and (**C**) Clara cell 16 protein.*

Table 4.5: *Correlations between pulmonary vascular resistance index and transpulmonary biomarker gradients*

	PVRi before protamine	
Variable	Correlation coefficient	*p* value
Transpulmonary elastase [μg/mL]	0.393	0.026
Transpulmonary CC16 [ng/mL]	0.421	0.016

vascular resistance index showed a small beneficial effect for the pulsatile group, in that it did not exceed baseline values, whereas the control group showed almost a 50% increase two hours after arrival in the ICU.

The topic of pulsatile flow is one with much controversy. In this study, 37 patients were randomly assigned to either perfusion with the centrifugal pump in pulsatile mode or in continuous mode. However, when the pump was in pulsatile mode this did not seem to be associated with marked clinical benefits. This is in accordance with a recent study in which the clinical effectiveness of pulsatile flow, induced by a centrifugal pump, was assessed [13]. The authors, although not specifically looking into lung function, did not find any difference in clinical outcomes. On the other hand, our results are in contrast to those of Onorati *et al*, who showed that COPD patients that received pulsatile flow during CABG had less ventilation time, better PaO_2/FiO_2, and better respiratory-system compliance following surgery [7]. In their study, a roller pump in combination with an intra-aortic balloon pump was used to create pulsatile flow. In their control group the IABP was turned off, resulting in standard linear flow. When we compare their results to those of the present study we see some similarities and some differences. The mechanical ventilation time in the present study was not different between study groups and was comparable to the control group from their study. However, in their group with IABP-induced pulsatile flow, the mechanical ventilation time was almost reduced by 40%. When looking at the oxygenation (PaO_2/FiO_2), we saw a drop at the end of surgery in both study groups in the present study, which was again comparable to the control group of Onorati *et al*. Their group with IABP-induced pulsatile flow, however, did not display a drop in PaO_2/FiO_2 but demonstrated a small increase at the end of surgery, which lasted throughout the entire postoperative course. These differences in observations are most probably explained by the method of producing pulsatile flow, as the literature shows that IABP pumping can generate larger differences (up to 23.3%) between MAP and EEP [14] as compared with the present set-up (7.0%). Unfortunately, in the study of Onorati *et al* these values were not reported. To ascertain if it is the method of producing pulsatile flow or merely the difference between MAP and EEP generated by the pulsatile flow that is responsible for better lung function preservation,

a study that compares these methods directly would be of interest. Another factor that could ex- plain the differences between the present study and the study of Onorati *et al* is the difference in average age of both study populations. In the present study the patients were, on average, 10 years older and it is known that arterial stiffness increases with age [15], which could mean that younger patients would benefit more from pulsatile flow than older patients.

The use of lung epithelium specific secretory proteins for evaluating the integrity of the alveolar capillary membrane is an alternative method to assess lung injury [16]. Serum CC16 concentrations have been associated with bronchiolitis obliterans syndrome (BOS) after lung transplantation [17] and primary graft dysfunction after lung transplantation [18]. Additionally, CC16 has been utilized as a lung injury marker for comparison of mechanical ventilation strategies during various surgical procedures [19] and for comparison of a mini-extracorporeal circuit versus a conventional cardiopulmonary bypass system [20, 21]. More recently, we have shown that CC16 concentrations correlate with pulmonary dysfunction (alveolar arterial oxygen gradient) during cardiothoracic surgery and that it was possible to differentiate between off-pump and on-pump coronary artery bypass grafting [22]. Surfactant protein plasma concentrations are associated with sepsis, respiratory distress syndrome and interstitial lung diseases [23]. More recently, Agostoni *et al* evaluated SP-B as a lung injury marker after elective coronary artery bypass grafting with the use of cardiopulmonary bypass [24]. Immediately after surgery, they found a fourfold increase of SP-B, which returned to baseline within 48 h. The authors concluded that SP-B could be a sensitive and rapid biomarker of lung distress.

When looking at a subclinical level of lung injury by means of biomarkers, we again observed no difference between continuous or pulsatile perfusion. The biomarkers were all elevated immediately after surgery and declined again during the first 24 h. An additional method for measuring lung injury by means of biomarkers was performed by drawing blood samples before and after the lungs and by establishing a concentration gradient between these two blood samples. These blood samples were taken right after the start of reperfusion, which means that the increase in serum biomarker concentrations could be ascribed to lung ischemia/reperfusion injury. Although these gradients were not different between groups, it was of interest that we observed a significant correlation between the PVRi and the transpulmonary gradient in elastase and the transpulmonary gradient in CC16. This could be explained when the increase in elastase is the result of a neutrophil influx during ischemia, since it is known that neutrophillic enzymes, such as elastase, produce diffuse tissue injury and result in increased pulmonary vascular permeability [2]. This, in turn, would lead to an increase in pulmonary vascular resistance. Although this method has its logistical disadvantages, it is very suitable to analyze the release of biochemical markers from a single organ, and, in this case, the lungs.

Pulmonary dysfunction following CPB is a well-known problem and is characterized by functional, physiological, biochemical, and histological changes [1]. In these elderly patients we found a transient lung impairment by means of clinical and biochemical variables. Pulsatile flow is thought to be beneficial in preventing lung injury by means of better perfusion of the bronchial artery. The advantages of bronchial artery perfusion have been demonstrated in a porcine model in which the bronchial artery was actively perfused by connecting it to the CPB circuit [25]. The authors showed that by active perfusion of the bronchial artery, detrimental metabolic and ultrastrutural changes of lung tissue where significantly reduced. Furthermore, they showed a reduction of inflammatory substances in bronchoalveolar lavage fluid.

The limitations of this study that should be acknowledged are, first, the relatively small number of patients that was included. The power of our study is therefore limited. Second, the patient group consisted of elderly patients (≥75 years) and, as is known, aortic stiffness increases with age [15]. This means that a larger difference between MAP and EEP may be necessary to see any beneficial effects of pulsatile flow and that a younger patient group could benefit more from the present set-up.

In our study, the extra energy generated with pulsatile flow should in theory result in better perfusion of the capillaries, supplying more oxygenated blood, antioxidants, and/or nutrients to the ischemic lung. However, we were not able to show any beneficial effects of pulsatile flow, except for a lower pulmonary vascular resistance. That we did not observe a beneficial effect could be attributed to the limited pulsatility. In conclusion, in our study pulsatile flow did not seem beneficial on postoperative lung function in elderly patients. Moreover, pulsatile flow did not affect lung function on a subclinical level as assessed by lung biomarkers.

References

[1] Ng CSH, Wan S, Yim APC, Arifi AA. Pulmonary dysfunction after cardiac surgery. Chest. 2002;121(4):1269–77.

[2] Wan S, LeClerc JL, Vincent JL. Inflammatory Response to Cardiopulmonary Bypass: Mechanisms Involved and Possible Therapeutic Strategies. Chest. 1997;112(3):676–692.

[3] Ji B, Undar A. An evaluation of the benefits of pulsatile versus nonpulsatile perfusion during cardiopulmonary bypass procedures in pediatric and adult cardiac patients. ASAIO Journal. 2006;52(4):357–61.

[4] Alghamdi AA, Latter DA. Pulsatile versus nonpulsatile cardiopulmonary bypass flow: an evidence-based approach. Journal of Cardiac Surgery. 2005;21(4):347–54.

[5] Schlensak C, Doenst T, Preusser S, Wunderlich M, Kleinschmidt M, Beyersdorf F. Bronchial artery perfusion during cardiopulmonary bypass does not prevent ischemia of the lung in piglets: assessment of bronchial artery blood flow with fluorescent microspheres. European Journal of Cardio-Thoracic Surgery. 2001;19(3):326–31.

[6] Dodd-o JM, Welsh LE, Salazar JD, Walinsky PL, Peck EA, Shake JG, et al. Effect of bronchial artery blood flow on cardiopulmonary bypass-induced lung injury. American Journal of Physiology - Heart and Circulatory Physiology. 2004;286(2):H693–700.

[7] Onorati F, Cristodoro L, Bilotta M, Impiombato B, Pezzo F, Mastroroberto P, et al. Intraaortic balloon pumping during cardioplegic arrest preserves lung function in patients with chronic obstructive pulmonary disease. The Annals of Thoracic Surgery. 2006;82(1):35–43.

[8] Onorati F, Santarpino G, Presta P, Caroleo S, Abdalla K, Santangelo E, et al. Pulsatile perfusion with intra-aortic balloon pumping ameliorates whole body response to cardiopulmonary bypass in the elderly. Critical Care Medicine. 2009;37(3):902–11.

[9] Santini F, Onorati F, Telesca M, Patelli F, Berton G, Franchi G, et al. Pulsatile pulmonary perfusion with oxygenated blood ameliorates pulmonary hemodynamic and respiratory indices in low-risk coronary artery bypass patients. European Journal of Cardio-Thoracic Surgery. 2011;40(4):794–803.

[10] Curtis JJ, Walls JT, Boley TM, Schmaltz RA, Demmy TL, Salam N. Coronary revascularization in the elderly: determinants of operative mortality. The Annals of Thoracic Surgery. 1994;58(4):1069–72.

[11] Shepard RB, Simpson DC, Sharp JF. Energy equivalent pressure. Archives of Surgery. 1966;93(5):730–40.

[12] Undar A. Myths and truths of pulsatile and nonpulsatile perfusion during acute and chronic cardiac support. Artificial Organs. 2004;28(5):439–43.

[13] Gu YJ, van Oeveren W, Mungroop HE, Epema AH, den Hamer IJ, Keizer JJ, et al. Clinical effectiveness of centrifugal pump to produce pulsatile flow during cardiopulmonary bypass in patients undergoing cardiac surgery. Artificial Organs. 2011;35(2):E18–26.

[14] Lim CH, Son HS, Fang YH, Lee JJ, Baik KJ, Kim KH, et al. Hemodynamic energy generated by a combined centrifugal pump with an intra-aortic balloon pump. ASAIO Journal. 2006;52(5):592–4.

[15] Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita Ja, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004;43(6):1239–45.

[16] Hermans C, Bernard A. Lung epithelium-specific proteins: characteristics and potential applications as markers. American Journal of Respiratory and Critical Care Medicine. 1999;159(2):646–78.

[17] Nord M, Schubert K, Cassel TN, Andersson O, Riise GC. Decreased serum and bronchoalveolar lavage levels of Clara cell secretory protein (CC16) is associated with bronchiolitis obliterans syndrome and airway neutrophilia in lung transplant recipients. Transplantation. 2002;73(8):1264–9.

[18] Diamond JM, Kawut SM, Lederer DJ, Ahya VN, Kohl B, Sonett J, et al. Elevated plasma clara cell secretory protein concentration is associated with high-grade primary graft dysfunction. American Journal of Transplantation. 2011;11(3):561–7.

[19] Determann RM, Millo JL, Waddy S, Lutter R, Garrard CS, Schultz MJ. Plasma CC16 levels are associated with development of ALI/ARDS in patients with ventilator-associated pneumonia: a retrospective observational study. BMC Pulmonary Medicine. 2009;9:49.

[20] van Boven W, Gerritsen W, Waanders F, Haas F, Aarts L. Mini extracorporeal circuit for coronary artery bypass grafting: initial clinical and biochemical results. Perfusion. 2004;19(4):239–246.

[21] van Boven WJP, Gerritsen WBM, Zanen P, Grutters JC, van Dongen HPA, Bernard A, et al. Pneumoproteins as a lung-specific biomarker of alveolar permeability in conventional on-pump coronary artery bypass graft surgery vs mini-extracorporeal circuit: a pilot study. Chest. 2005;127(4):1190–5.

[22] Engels GE, Gu YJ, van Oeveren W, Rakhorst G, Mariani MA, Erasmus ME. The utility of lung epithelium specific biomarkers in cardiac surgery: a comparison of biomarker profiles in on- and off-pump coronary bypass surgery. Journal of Cardiothoracic Surgery. 2013;8(1):4.

[23] Sorensen GL, Husby S, Holmskov U. Surfactant protein A and surfactant protein D variation in pulmonary disease. Immunobiology. 2007;212(4-5):381–416.

[24] Agostoni P, Banfi C, Brioschi M, Magrì D, Sciomer S, Berna G, et al. Surfactant protein B and RAGE increases in the plasma during cardiopulmonary bypass: a pilot study. European Respiratory Journal. 2011;37(4):841–7.

[25] Schlensak C, Doenst T, Preusser S, Wunderlich M, Kleinschmidt M, Beyersdorf F. Cardiopulmonary bypass reduction of bronchial blood flow: A potential mechanism for lung injury in a neonatal pig model. The Journal of Thoracic and Cardiovascular Surgery. 2002;123(6):1199–1205.