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Pulsatile Cardiopulmonary Bypass With Intra-Aortic Balloon Pump Improves Organ Function and Reduces Endothelial Activation

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Background: We aimed to evaluate if the use of an intra-aortic balloon pump (IABP) during cardioplegic arrest improves organ function and reduces endothelial activation in patients undergoing coronary artery bypass graft (CABG).

Methods and Results: Five-hundred and one CABG patients were randomized into 2 groups: (Group A n=270) linear cardiopulmonary bypass (CPB); and (Group B n=231) automatic 80 beats/min IABP-induced pulsatile CPB. We evaluated hemodynamic response, coagulation and fibrinolysis, transaminase, bilirubin, amylase, lactate, renal function (estimated glomerular filtration rate [eGFR], creatinine and any possibility of renal insufficiency or failure), respiratory function and endothelial markers (vascular endothelial growth factor [VEGF] and monocyte chemotactic protein-1 [MCP-1]). IABP, which induced surplus hemodynamic energy, was 21,387±4,262 ergs/cm^3. Group B showed lower chest drainage, transfusions, international normalized ratio, and antithrombin III, together with higher platelets, activated partial thromboplastin time, fibrinogen and D-dimer. Transaminases, bilirubin, amylase, lactate were lower in Group B; there were better results for eGFR in Group B from ICU-arrival to 48 h, resulting in lower creatinine from ICU-arrival to 48 h. The necessity for renal replacement therapy was lower in Group B Stage-3. Group B P_aO_2/F_iO_2 and lung compliance improved with aortic de-clamping on the first day with shorter intubation time. Group B showed lower VEGF and MCP-1.

Conclusions: Pulsatile flow by IABP improves whole-body perfusion and reduces endothelial activation during CPB. (*Circ J* 2012; **76:** 1121–1129)

Key Words: Cardiopulmonary bypass; Coronary heart disease; Inflammation

Despite increasing competition from percutaneous interventions and other novel methods of non-surgical coronary revascularization, coronary artery bypass grafting (CABG) remains a definitive and durable treatment for coronary artery disease, especially for patients with extensive and diffuse disease.[1] In recent years the CABG procedure itself has undergone innovation and evolution.[2] The systemic inflammatory response following cardiopulmonary bypass (CPB) has been indicated as the main cause for postoperative morbidity and mortality in CABG patients.[2] Despite improvements in biomaterials, non-pulsatile flow and blood interaction with the artificial surfaces of extracorporeal circulation are known to trigger inflammation after CPB.[2] Nevertheless, non-pulsatile blood flow is considered an acceptable compromise to perform accurate coronary anastomoses in a surgical field where there is an absence of blood. However, pulsatile CPB remains an open issue: some studies have reported beneficial effects on microcirculation, metabolism, and organ function,[3–7] and our group has previously demonstrated beneficial effects in selected groups of patients.[8] On the other hand, others have not observed any superiority with pulsatile CPB.[9,10] Moreover, studies of endothelial activation following pulsatile and non-pulsatile perfusion have given contradictory results under the current terminology:[11–14] some studies report beneficial effects of pulsatile perfusion on endothelial response to CPB,[12–14] but others did not find any superiority of pulsatile CPB over non-pulsatile perfusion.[11]

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However, the terminology lacks studies of pulsatile vs. non-pulsatile perfusion in non-selected populations undergoing CABG. Therefore, the aim of this study, based on wider experience, was to evaluate hemodynamic response, organ and metabolic functions and biomolecular markers of endothelial activation in CABG patients undergoing intra-aortic balloon pump (IABP)-induced pulsatile CPB vs. standard linear non-pulsatile CPB.

Methods

Patients and Study Design

Between January 2004 and February 2010, we prospectively enrolled 501 patients undergoing isolated primary CABG with the need for a preoperative IABP. All patients were scheduled for preoperative IABP because of cardiac indications, as already reported,[8] and were also considered at risk for a preoperative ischemic event, which included any of the following: critical left main disease with occlusion ≥90% ±poor left ventricular ejection fraction (LVEF <40%); severe left mainstem lesion ≥75% with severe right coronary stenosis ≥90%; severe depression of the LVEF (<25%) regardless of the severity of any of the coronary lesions. Patients were randomized by lottery, drawing out pre-prepared sealed envelopes containing the group assignment: 270 patients (Group A) received preoperative IABP treatment before induction of anesthesia, with IABP turned off during cardioplegic arrest, and restarted with a 1:1 IABP mode immediately after cross-clamp removal, following the traditional standard of care; the other 231 patients (Group B) received preoperative IABP, as described earlier, which was then switched to an automatic 80 beats/min mode during cross-clamping (in order to achieve pulsatile flow during aortic cross-clamping) and switched again to a 1:1 IABP mode after cross-clamp removal.[8]

Institutional Review Board/Ethics Committee approval was obtained (September 2003). Informed consent was given by each patient.

Exclusion Criteria

In order to avoid misleading data, 43 patients admitted during the same time period were excluded from the study because of isolated or combined severe splanchnic organ comorbidities: renal failure in 16 patients, liver failure in 7, abdominal aortic aneurysm with abdominal artery vasculopathy in 7, severe autoimmune disease in 3 and preexisting hematologic and coagulative disorders in 10.

Anesthesia

Inotropes were immediately put into effect after aortic cross-clamp removal to maintain adequate mean systemic pressure, starting in all cases with enoximone at a dosage of $5\,\mu g \cdot kg^{-1} \cdot min^{-1}$, according to the institutional policy.[8] The need for a further increase in inotropes was established in order to maintain mean arterial pressure >65 mmHg with a central SvO_2 >60%, after optimization of the preload.[8] Inotropic support was recorded and defined as "low-dose" when enoximone was administered at $\leq 5\,\mu g \cdot kg^{-1} \cdot min^{-1}$; "medium-dose" when enoximone was between 6 and $10\,\mu g \cdot kg^{-1} \cdot min^{-1}$, or dobutamine was added at a dosage between 5 and $10\,\mu g \cdot kg^{-1} \cdot min^{-1}$; or "high-dose" when enoximone or dobutamine infusion was $>10\,\mu g \cdot kg^{-1} \cdot min^{-1}$ or epinephrine at any dose was added.[8]

Surgical Technique and CPB

To aid hemodynamic function before CABG and to avoid the sudden occurrence of myocardial ischemia during the induction phase, institutional policy called for percutaneous insertion of the IABP using a sheathless technique (7–7.5Fr; 34 or 40 ml according to the body surface area; balloon, Datascope Corp, Fairfield, NJ, USA) through the most appropriate femoral artery before induction of anesthesia, connected to a Datascope pump (Datascope Corp). CPB and surgical techniques were standardized and did not change during the study period. The same senior surgeon performed a full sternotomy in all cases of surgery. CPB was standardized: a Dideco (Mirandola, Modena, Italy) tubing set, which included a 40-micron filter, a Stockert non-pulsatile roller pump (Stockert Instrumente, Munich, Germany) and a hollow fiber membrane oxygenator (Monolyth, Sorin Biomedica, Saluggia, Italy). Heparin was induced at a dose of 300 IU/kg to achieve a target activated clotting time >480 s. Systemic temperature was kept between 32°C and 34°C. The ascending aorta remained clamped below the brachiocephalic artery. Myocardial protection was always achieved with antegrade warm blood cardioplegia at intermittent retrograde maintenance every 15 min. Total CPB flow was maintained at $2.6\,L \cdot min^{-1} \cdot m^{-2}$. In Group A, IABP was turned off during cardioplegic arrest, maintaining a standard non-pulsatile CPB; Group B patients underwent IABP-induced pulsatile CPB during cardioplegic arrest, with pulsatile flow maintained by an automatic 80 beats/min mode until aortic de-clamping. Surplus hemodynamic energy induced by IABP was recorded according to the method of Travis et al.[4] Protamine was administered at the end of the operation to fully reverse heparin. Blood recovery using an autotransfusion device (Autotrans Dideco, Mirandola, Modena, Italy) was performed intraoperatively in all cases. A level of hemoglobin <7 g/dl was considered a mandatory indication for blood transfusion in the intraoperative period or in the immediate 48 h postoperatively. Levels of hemoglobin <8 g/dl suggested blood transfusion postoperatively only in the presence of organ dysfunction. Following surgery, patients received enoxaparin for anticoagulation, with a target activated partial thromboplastin time (aPTT) >40 s, starting when the postoperative bleeding was controlled (usually within 6 h) until the 3rd postoperative day. Starting from the 3rd postoperative day, 150 mg of acetylsalicylic acid was administered daily. IABP was withdrawn when hemodynamic stability was restored.

Endpoints

Staff caring for the patients in the intensive care unit (ICU) during the postoperative course were unaware of the intraoperative group assignment. Changes in organ and metabolic functions for the splanchnic, respiratory, and hemocoagulative systems and evaluation of the endothelial response secondary to the 2 types of CPB were the main focus of the study. The primary endpoints for the evaluation of the renal function were perioperative changes in estimated glomerular filtration rate (eGFR) (calculated preoperatively and daily thereafter and used to stratify the renal risk profile of the patients, which was divided into Stage 1–2 and Stage 3 KDOQI (Kidney Disease Outcomes Quality Initiative)[8]) and creatinine clearance, whereas daily diuretic dose, incidence of renal failure and serum creatinine were secondary endpoints. Creatinine clearance was calculated preoperatively, at the end of CPB, at ICU-arrival, and on the 1st and 2nd postoperative days, using the Cockroft-Gault formula: creatinine clearance=(140−age) ×weight (kg)/(serum creatinine×72 (×0.85 for women)). Acute renal insufficiency (ARI) was defined >50% increase over the

preoperative serum creatinine value, whereas renal failure was defined as any postoperative renal insufficiency requiring renal replacement therapy. Perioperative alanine aminotransferase (ALT) leakage was the primary endpoint to evaluate the liver's response to CPB. Amylase leakage was the primary endpoint to evaluate pancreatic function. Postoperative ileus (defined as a delay in gut motility >72 h), liver injury (defined as an acute increase in serum ALT level >500 IU/L within 48 h of surgery), aspartate aminotransferase (AST), lactic dehydrogenase, and bilirubin (total and fractioned) leakages were secondary endpoints to investigate perioperative mesenteric, liver, and pancreatic function, respectively. Biochemical serum markers of the splanchnic system were sampled preoperatively, at ICU admission, and on the 1st and 2nd postoperative days. Blood lactate samples were taken preoperatively, at the end of CPB, at ICU-arrival, and on the 1st postoperative day as a marker of peripheral metabolic state. Respiratory function was primarily investigated by the ratio of arterial oxygen tension to inspired oxygen fraction (P_aO_2/F_iO_2), measured preoperatively, at aortic de-clamping, at admission to ICU, and at 24 and 48 h. Arterial blood gas analysis (GEM Premier 3000 analyzer, Lexington, MA, USA) was performed with the samples obtained from the peripheral systemic artery. Secondary respiratory endpoints were: (1) intubation time, defined as the time interval between orotracheal intubation and extubation; extubation was performed when the patient was awake, eupnoic, cooperative, with respiratory rate <30/min, hemo-gas analysis demonstrated acid–balance equilibrium with PEEP support ≤5 mm/Hg and F_iO_2 ≤0.5, and mediastinal drainage ≤100 ml/h; (2) respiratory system compliance (RSC) was expressed in ml/cmH_2O, and measured via the mechanical ventilator (Evita 4, Dräger Medizintechnik Gmbh, Lubeck, Germany) preoperatively, at the end of surgery, and at 4 and 8 h postoperatively; (3) scoring of chest radiographs (SCR) performed preoperatively, at admission to ICU, and at 24 and 48 h postoperatively by a radiologist according to the lung injury score, proposed by Murray et al,[15] ranging from 0 (no infiltrate) to 4 (extensive alveolar consolidation); (4) need for non-invasive positive-pressure ventilation (NIV). Postoperative chest drainage was primarily investigated with regard to the hemocoagulative response to the 2 types of CPB. Chest drains were collected for total drainage during the 1st postoperative day, total drainage during the 2nd postoperative day, and another total amount until they were withdrawn (usually on the 3rd postoperative day according to institutional policy). Hemocoagulative parameters were secondary endpoints: peripheral red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), hematocrit (Hct), aPTT, international normalized ratio (INR), fibrinogen, antithrombin III (AT-III) activity and D-dimer (latex immunoturbidimetric assay; Boehringer-Mannheim, Marburg, Germany), were measured at hospital admission, at admission to the ICU and at 12, 24 and 48 h postoperatively. Blood samples were collected at intervals from a peripheral vein. In order to avoid bias from hemodilution, the PLT, fibrinogen, and D-dimer values were analyzed checking for hemodilution using the formula: $(Sample_{corrected})_{timeX}=(Sample)_{timeX}\times(Hct)_{baseline-time}/(Hct)_{timeX}$. Data on the need for re-exploration for bleeding, and transfusions were similarly collected. Transfusions were registered as red blood cell, fresh frozen plasma and platelets units per patient.

In the last 60 patients enrolled in the study protocol, we started to evaluate the endothelial response to CPB as perioperative changes in the monocyte chemotactic protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) levels. Blood was collected from the peripheral arterial line preoperatively, immediately before aortic de-clamping, at the end of surgery, and after 12 and 24 h postoperatively. MCP-1 and VEGF levels were simultaneously and quantitatively determined by sandwich chemiluminescent immunoassay from Biochip Array Technology (Randox, UK). All assays were performed according to the manufacturer's instructions.

In-hospital mortality, morbidity, in-hospital and ICU stay, IABP-related complications were registered. Perioperative acute myocardial infarction (AMI) was defined when new Q waves >0.04 ms, and/or a reduction in R waves (>25% in at least 2 leads) were detected, and a new akinetic/dyskinetic segment was identified at echocardiography, TnI peaked at 3.1 μg/L at 12 h; perioperative myocardial damage (MD) as TnI peak >3.1 μg/L at 12 h with at least minor ECG changes and without new akinetic/dyskinetic segments at echocardiography, as previously reported.[8]

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 15.0 (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean±standard error, and categorical variables are presented as absolute numbers and/or percentages. Data was checked for normality before statistical analysis with the Kolmogorov-Smirnov test. Normal distributed continuous variables were compared using the unpaired t-test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the chi-square test or Fischer's exact test. Comparison between and within groups was made using a 2-way analysis of variance for repeated measures. Between and within interactions of 5-time measurements in 20 patients for each study arm gave a priority power (1-β error probability) of 98% with an α-error probability of 0.05. Comparisons were considered significant when P<0.05.

Results

The 2 groups proved homogeneous for preoperative and intraoperative variables (Table 1).

Hemodynamic Results, Hospital Mortality, and IABP-Related Complications

Need for intraoperative vasoconstrictors did not differ between the 2 groups (Table 1). IABP-induced surplus hemodynamic energy was 21,387±4,262 ergs/cm^3. There were 12 hospital deaths, 6 for each group (2.2% vs. 2.6%; P=0.78), because of postoperative low output syndrome in 8 patients, multi-organ failure following deep sternal wound infection in 4; 5 patients in Group A developed perioperative AMI requiring prolonged IABP assistance for more than 72 h (1.9% vs. Group B: 0%; P=0.07). Perioperative inotropic support was comparable between the 2 groups (low-dose Group A: 114/270–42.2% vs. Group B 105/231–45.5%; P=0.47; medium-dose Group A: 108/270–40% vs. Group B 91/231–39.4%; P=0.93; high doses Group A 48/270–17.8% vs. Group B: 35/231–15.2%; P=0.47). Mean in-ICU stay (Group A: 2.4±0.1 days vs. Group B: 2.1±0.2; P=0.15) and hospital stay (Group A: 7.8±0.3 days vs. Group B: 7.0±0.2; P=0.769) were similar.

When IABP-related complications were considered, there were 4 transient limb ischemia (0.8% of global population; 3 [1.1%] Group A vs. 1 [0.4%] Group B, P=0.395), which completely recovered following prompt withdrawal of IABP.

Table 1. Patient Demographic and Intraoperative Data

	Group A (n=270)	Group B (n=231)	P value
Age (years)	68.2±1.12	69.7±0.95	0.24
Sex (male)	213/270 (78.9%)	176/231 (76.2%)	0.52
Diabetes	132/270 (48.9%)	121/231 (52.4%)	0.47
Smoker	110/270 (40.7%)	97/231 (42.0%)	0.79
Hypertension	98/270 (36.3%)	97/231 (42.0%)	0.20
Hyperlipidemia	63/270 (23.3%)	52/231 (22.5%)	0.83
COPD	89/270 (32.9%)	93/231 (40.6%)	0.09
Previous AMI	98/270 (36.3%)	89/231 (38.5%)	0.64
Recent AMI (<4 weeks)	81/270 (30%)	86/231 (37.2%)	0.09
LVEF <40%	233/270 (86.3%)	185/231 (80.1%)	0.07
WMSI (mean ± SD)	1.52±0.34	1.50±0.47	0.67
β-blockers	165/270 (61.1%)	126/231 (54.5%)	0.15
ACE inhibitors	172/270 (63.7%)	138/231 (59.7%)	0.41
Furosemide	220/270 (81.5%)	193/231 (83.5%)	0.56
Aortic cross-clamp time (min)	48.3±1.02	49.2±0.67	0.43
CPB time (min)	91.6±1.53	93.4±1.68	0.68
Total operation time (min)	132.3±10.7	139.9±12.1	0.79
No. of grafts (mean ± SD)	3.24±0.3	3.15±0.2	0.96
Total arterial grafting	67/270 (24.8%)	59/231 (25.5%)	0.92
Intraoperative defibrillation	36/270 (13.3%)	34/231 (14.7%)	0.70
Need for intraoperative vasoconstrictors	13/270 (4.8%)	9/231 (3.9%)	0.67

COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; WMSI, wall motion score index; CPB, cardiopulmonary bypass.

Table 2. Analysis of Renal Function

	Pre-CPB	End-CPB	ICU	1st POD	2nd POD	P**	P†
Creatinine clearance (ml/min)							
Group A	69.2±1.5	59.2±0.8	52.3±1.8	52.8±1.6	55.4±1.8	0.427	0.001
Group B	68.3±0.9	67.1±1.4	63.6±0.9	65.3±1.1	68.1±1.3	0.351	
P*	0.722	0.001	0.001	0.001	0.001	–	
Serum creatinine (mg/dl)							
Group A	1.1±0.2	1.5±0.09	1.6±0.02	1.5±0.21	1.7±0.14	0.28	0.001
Group B	1.0±0.1	1.1±0.03	1.3±0.05	1.1±0.07	1.1±0.02	0.32	
P*	0.51	0.001	0.001	0.001	0.001	–	
Daily furosemide (mg)							
Group A	22.7±1.4	22.3±0.9	43.2±1.3	52.1±0.7	46.4±1.5	0.001	0.001
Group B	23.8±1.3	18.3±0.8	24.1±1.2	27.9±1.1	22.6±0.9	0.29	
P*	0.37	0.001	0.001	0.001	0.001		

*Statistical probability at each time point; **statistical probability within group; †statistical probability between groups. CPB, cardiopulmonary bypass; ICU, intensive care unit; POD, postoperative day.

Splanchnic Organ and Metabolic Functions

Group B showed significantly better creatinine clearance at all time points compared with Group A (Table 2). It is evident that Group B showed an almost preserved creatinine clearance following surgery, whereas Group A demonstrated a progressive decline. These results correlated with lower serum creatinine (Table 2). Accordingly, the daily furosemide dose was higher in Group A (Table 2). The prevalence of ARI was significantly lower in Group B (36/231–15.6% vs. Group A 85/270–31.5%; P<0.001), whereas the incidence of ARF requiring renal replacement therapy was similar (12/231–5.2% vs. Group A 21/270–7.8%; P=0.28). According to the KDOQI classification, 177 patients in Group A (65.6%) and 154 in Group B (66.7%) were in Stages 1–2 (P=0.85), while the remaining 93 in Group A (34.4%) and 77 in Group B (33.3%) were in Stage 3 (P=0.85). In the subgroup analysis of patients stratified according to preoperative KDOQI stage of renal disease, both the patients in Stages 1–2 and those in Stage 3 showed better preserved eGFR and creatinine values from ICU-arrival to 48 h postoperatively whenever pulsatile perfusion was used (Table 3). Moreover, the incidence of renal insufficiency and need for renal replacement therapy was lower in Group B Stage-3 (Table 3).

Biochemical markers of liver and pancreatic function always proved to be lower in Group B (Table 4). Subsequently, lactate levels were lower in Group B (Table 4). There were 8 cases of postoperative ileus (5/270 patients–1.9% in Group A vs. 3/231–1.3% in Group B; P=0.73), which successfully resolved following IABP withdrawal, fenoldopam administration and re-hydration.

Table 3. Perioperative eGFR and Creatinine Level and Rates of ARI and ARF in Patients With Preoperative KDOQI Stages 1–2 and 3 Kidney Disease

	Preoperative	ITU	24 h	48 h	P**	P†
eGFR (ml/min)						
Stages 1–2						
Group A	98±2.1	75±1.7	67±1.5	68±1.9	0.021	0.001
Group B	99±1.8	92±1.5	90±1.1	92±1.4	0.49	
P*	0.32	0.001	0.001	0.001	–	
Stage 3						
Group A	53±1.4	47±1.3	41±1.8	40±1.5	0.005	0.001
Group B	54±1.2	52±1.6	49±1.4	57±1.6	0.07	
P*	0.51	0.003	0.001	0.001	–	
Creatinine (mg/dl)						
Stage 1–2						
Group A	0.8±0.03	1.3±0.05	1.2±0.09	1.2±0.09	0.72	0.001
Group B	0.9±0.02	0.9±0.04	1.0±0.03	0.9±0.02	0.85	
P*	0.82	0.001	0.001	0.001	–	
Stage 3						
Group A	1.6±0.12	1.9±0.18	2.0±0.19	1.9±0.19	0.044	0.05
Group B	1.5±0.09	1.3±0.12	1.3±0.15	1.5±0.06	0.92	
P*	0.78	0.048	0.014	0.018	–	
	Perioperative ARI	**P value**				
Stage 1–2						
Group A	21/177 (11.9%)	0.34				
Group B	24/154 (15.6%)					
Stage 3						
Group A	64/93 (68.8%)	<0.001				
Group B	13/77 (16.9%)					
	Perioperative ARF	**P value**				
Stage 1–2						
Group A	2/177 (1.1%)	0.26				
Group B	5/154 (3.2%)					
Stage 3						
Group A	19/93 (20.4%)	0.028				
Group B	6/77 (7.8%)					

*Statistical probability at each time point; **statistical probability within group; †statistical probability between groups. eGFR, estimated glomerular filtration rate; ARI, acute renal injury; ARF, acute renal failure; KDOQI, Kidney Disease Outcomes Quality Initiative.

Respiratory Results

Functional markers of respiratory function, such as P_aO_2/F_iO_2 and RSC, were significantly better in Group B (Table 5). Patients undergoing linear CPB demonstrated a gradual decrease of oxygenation during the entire surgical period, reaching the pre-CPB values only on the 2nd postoperative day. On the other hand, P_aO_2/F_iO_2 showed an early improvement at aortic de-clamping in patients undergoing pulsatile perfusion, and maintained a better, or at least the same preoperative value, during the entire postoperative course. RSC worsened in both groups after CPB, with a slow but progressive improvement in the first few hours after surgery. Again, patients undergoing pulsatile CPB showed better values at the end of surgery, and a greater improvement at 4 and 8 h postoperatively. SCR demonstrated progressive worsening in Group A, not in Group B (Table 5). Therefore, intubation time (13.2±1.4 h vs. Group A: 16.9±1.1; P=0.027) and the need for NIV were lower in Group B (36/231–15.6% vs. Group A 85/270–31.5%; P<0.001).

Hemocoagulative Results

Less chest drainage (1st day: Group A 689±38 ml vs. Group B 386±12, P=0.001; 2nd day: 451±18 vs. 171±12, P=0.001; total drainage: 1.98±72 vs. 615±41, P=0.001) and need for transfusion were observed following pulsatile perfusion (packed RBCs: Group A 2.45±0.31 units vs. Group B 0.45±0.18 units, P=0.001; fresh frozen plasma: 0.41±0.18 vs. 0.20±0.09, P=0.001; platelets: 0.33±0.02 vs. 0.07±0.01, P=0.02). Accordingly: (1) Group B showed a slightly higher RBC count, but significantly higher Hct and PLT, together with a lower WBC increase during the whole postoperative time-course (Table 6); (2) less activation and consumption of the coagulative system was detected in Group B. In particular, Group A patients demonstrated a significant fall in perioperative fibrinogen, whereas patients undergoing IABP-induced pulsatile CPB demonstrated a non-significant reduction of fibrinogen at the end of surgery, which remained stable during the following postoperative course (Table 6). INR rapidly increased at the end of surgery and at 12 h postoperatively in Group A, but not in Group B. Finally, despite the fact that aPTT proved longer in both groups, its value was significantly higher in Group A (Table 6); (3) Group A demonstrated a higher activation of the fibrinolytic system, as shown by a constant higher D-dimer

Table 4. Metabolic Data

	Preoperative	ICU	1st POD	2nd POD	P**	P†
ALT (U/L)						
Group A	20.8±1.74	32±1.91	28.5±1.22	23.7±1.74	0.001	0.001
Group B	19.2±1.23	19.9±1.23	18.1±1.01	16.9±0.82	0.001	
P*	0.49	0.001	0.001	0.001	–	
AST (U/L)						
Group A	24.1±1.27	35.1±2.17	30.1±1.77	26.8±1.33	0.001	0.001
Group B	22.1±0.94	22.9±0.83	23.1±0.45	21.4±0.91	0.001	
P*	0.32	0.001	0.001	0.001	–	
Amylase (U/L)						
Group A	25.1±1.23	40.1±2.82	36.2±2.04	32.4±1.51	0.001	0.001
Group B	24.2±1.68	22.6±0.97	21.8±0.76	22.0±0.63	0.001	
P*	0.66	0.001	0.001	0.001	–	
Bilirubin (mg/dl)						
Group A	0.87±0.05	2.1±0.23	1.5±0.23	1.3±0.37	0.001	0.001
Group B	0.91±0.04	1.2±0.04	1.2±0.08	1.1±0.12	0.003	
P*	0.83	0.001	0.001	0.001		
	Preoperative	**End-CPB**	**ICU**	**1st POD**	**P****	**P†**
Lactate (mmol/L)						
Group A	1.1±0.2	2.5±0.5	1.9±0.6	1.8±0.2	0.001	0.001
Group B	1.2±0.1	1.3±0.2	1.2±0.1	1.3±0.1	0.001	
P*	0.71	0.001	0.001	0.001	–	

*Statistical probability at each time point; **statistical probability within group; †statistical probability between groups. ICU, intensive care unit; POD, postoperative day; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPB, cardiopulmonary bypass.

Table 5. Lung Function

	Preoperative	Aortic de-clamping	ICU	24 h	48 h	P**	P†
P_aO_2/F_iO_2 (mmHg)							
Group A	315.3±5.7	209.3±7.2	228.6±9.5	247.1±4.2	298±8.1	0.001	0.001
P_aO_2 (mmHg)	157.6	125	114.3	123.5	149		
P_aO_2/F_iO_2 (mmHg)							
Group B	313.8±4.2	367.1±8.1	324.3±6.9	356.1±7.3	481±11.2	0.001	
P_aO_2 (mmHg)	156.9	220.2	162.15	178	240		
P*	0.61	0.001	0.001	0.001	0.001		
	Preoperative	**End surgery**	**4 h**	**8 h**	**–**	**P****	**P†**
RSC (ml/cm H_2O)							
Group A	79.1±0.83	48.3±0.7	53.2±0.9	59.1±0.6	–	0.001	0.001
Group B	79.2±0.79	57.4±0.6	74.1±0.8	77.7±0.9	–	0.001	
P*	0.85	0.001	0.001	0.001	–		
	Preoperative	**ICU**	**24 h**	**48 h**	**–**	**P****	**P†**
SCR (Units)							
Group A	0.016±0.02	0.49±0.06	0.61±0.03	0.39±0.02	–	0.001	0.001
Group B	0.010±0.01	0.28±0.01	0.26±0.07	0.28±0.01	–	0.001	
P*	0.57	0.001	0.001	0.001	–		

*Statistical probability at each time point; **statistical probability within group; †statistical probability between groups. ICU, intensive care unit; RSC, respiratory system compliance; SCR, scoring of chest radiograph.

production and lower AT-III activity starting from the end of surgery until the 2nd postoperative day. Patients undergoing pulsatile CPB demonstrated a significant D-dimer production and reduction of AT-III only at the end of surgery (Table 6).

Endothelial Response

Markers of the endothelial response showed a completely different pattern between the 2 groups. In particular, patients undergoing linear CPB demonstrated a progressive increase in MCP-1, which reached the peak value at ICU admission, and then showed a progressive fall at 48 h postoperatively (Table 7). On the other hand, patients undergoing pulsatile CPB demonstrated an initial reduction of circulating MCP-1 at aortic de-clamping, followed by a progressive increase and reaching the peak value at 24 h postoperatively (Table 7). However, MCP-1 levels were significantly lower at T1 and

Table 6. Hemocoagulative Parameters

	Preoperative	ICU admission	12 h	24 h	48 h	P**	P†
RBC (×10⁶/μl)							
Group A	4.8±0.09	3.6±0.09	3.6±0.06	3.5±0.01	3.5±0.03	0.35	0.81
Group B	4.7±0.12	3.8±0.03	3.8±0.11	3.4±0.02	3.5±0.01	0.42	
P*	0.72	0.31	0.34	0.55	0.77	–	
WBC (×10³/μl)							
Group A	7.2±0.31	11.2±0.64	19.1±0.92	22.8±0.33	19.7±0.93	0.75	0.001
Group B	7.5±0.22	9.2±0.32	11.2±0.67	13.9±0.21	11.9±0.12	0.13	
P*	0.09	0.004	0.001	0.001	0.001	–	
Hct (g/dl)							
Group A	39.7±0.61	29.1±0.32	26.8±0.29	34.5±0.81	33.4±0.29	0.001	0.001
Group B	39.9±0.45	32.9±0.56	31.2±0.34	35.1±0.79	34.2±0.85	0.27	
P*	0.92	0.001	0.001	0.53	0.39	–	
PLT (×10³/μl)							
Group A	274±6.5	179±3.5	122±6.9	110±7.8	106±5.2	0.145	0.001
Group B	276±5.7	183±6.7	179±6.4	220±5.1	210±5.2	0.548	
P*	0.8	0.632	0.001	0.001	0.001	–	
aPTT (s)							
Group A	31.8±1.9	47.6±0.2	55.1±1.4	53.1±0.9	46.9±0.6	0.76	0.001
Group B	33.3±0.6	38.2±0.5	39.4±0.8	42.2±0.7	37.9±0.5	0.15	
P*	0.61	0.001	0.001	0.001	0.001	–	
INR							
Group A	0.8±0.1	1.8±0.2	1.9±0.1	1.7±0.1	1.5±0.2	0.12	0.001
Group B	0.9±0.1	1.2±0.1	1.2±0.1	1.1±0.2	1.0±0.1	0.78	
P*	0.57	0.001	0.001	0.001	0.001	–	
Fibrinogen (mg/dl)							
Group A	312.5±5.6	249.4±2.3	201.2±9.8	212.7±6.2	230.5±7.1	0.27	0.001
Group B	307.3±4.3	287.9±7.5	302.3±5.1	296.5±3.9	305±7.1	0.012	
P*	0.32	0.001	0.001	0.001	0.001	–	
AT-III (%)							
Group A	90±0.6	53±2.8	43±2.2	59±1.9	72±1.5	0.04	0.001
Group B	89±0.5	65±1.3	72±1.8	83±1.0	89±0.1	0.06	
P*	0.49	0.001	0.001	0.001	0.001	–	
D-dimer (μg/ml)							
Group A	0.6±0.03	4.4±0.29	5.2±0.32	2.8±0.13	1.7±0.04	0.04	0.001
Group B	0.6±0.02	1.5±0.04	1.4±0.12	1.2±0.05	0.9±0.03	0.33	
P*	0.96	0.001	0.001	0.001	0.001	–	

*Statistical probability at each time point; **statistical probability within group; †statistical probability between groups. ICU, intensive care unit; RBC, red blood cells; WBC, white blood cells; Hct, haematocrit; PLT, platelets; aPTT, activated plasma thromboplastin time; INR, international normalized ratio; AT-III, antithrombin III activity.

Table 7. Endothelial Response

	Preoperative	Aortic de-clamping	ICU	24 h	48 h	P**	P†
MCP-1 (pg/ml)							
Group A	128±3.4	312±13.9	406±19.8	259±9.7	185±6.3	0.001	0.001
Group B	131±2.2	102±16.5	198±18.3	232±9.1	169±4.7	0.01	
P*	0.68	0.001	0.001	0.34	0.46	–	
VEGF (pg/ml)							
Group A	13±0.3	223±9.3	54±12.1	15±4.6	19±3.1	0.001	0.001
Group B	15±0.2	126±4.5	27±6.7	12±5.2	25±2.7	0.01	
P*	0.71	0.001	0.001	0.68	0.47	–	

*Statistical probability at each time point; **statistical probability within group; †statistical probability between groups. ICU, intensive care unit; MCP, monocyte chemotactic protein-1; VEGF, vascular endothelial growth factor.

T2 in patients undergoing pulsatile perfusion, and proved to have a significantly lower leakage than in patients undergoing linear perfusion (between groups P=0.001).

When VEGF was considered, it showed a biphasic kinetic in both groups, with the first peak at aortic de-clamping followed by a second peak at 48 h postoperatively (Table 7). Again, aortic de-clamping and ICU-arrival levels were significantly higher in patients undergoing linear perfusion (Table 7), giving a significantly lower leakage in patients undergoing pulsatile CPB (between groups P=0.001).

Discussion

For some decades the non-pulsatile flow of standard CPB has been considered an acceptable compromise to perform accurate coronary anastomoses during surgery where there is an absence of blood. However, the theoretical benefits of pulsatile perfusion have to be considered, consisting of reduction of vasoconstrictive reflexes, optimized oxygen consumption, and reduction of tissue acidosis.[2,5,7] Therefore, when we analyzed the splanchnic organ protection, we found better preservation of renal function with pulsatile flow, also in patients at a higher risk of having renal complications, such as KDOQI Stage 3 (Table 3). Although certain preoperative drugs or disorders[15,16] may affect the preoperative kidney function, our data confirm some previous studies, such as those of Boucher et al[9] and German et al[17] who discovered that non-pulsatile flow is associated with renal hypoxia and acidosis. Moreover, Mukherjee et al demonstrated decreased tissue oxygen pressure in the renal medulla and increased local lactate level in non-pulsatile models.[5] Similarly, Hornick and Taylor observed that non-pulsatile CPB results in progressive systemic arterial vasoconstriction, leading to reduced renal perfusion and acidosis.[3] Similarly, lower leakage of pancreatic and hepatic enzymes was detected in patients undergoing pulsatile CPB. Our data agree with those of Saggau et al,[6] who demonstrated that pulsatile CPB preserves pancreatic function better than non-pulsatile CPB, and with those of Murray et al,[18] who showed a reduced incidence of elevated amylase leakage in patients undergoing pulsatile CPB. Furthermore, Pappas et al[7] and Chiu et al[20] found that pulsatile flow during CPB preserves hepatic function, lowering AST leakage.

Pulmonary dysfunction is reported to be a frequent complication of CPB.[20] Although the mechanisms behind CPB-induced lung injury are complex, the observation that maintenance of a finite pulmonary artery and bronchial artery blood flow during CPB attenuates lung injury have shown that ischemia-eperfusion injury may be the main mechanism of inflammatory lung damage.[20] Therefore, it can be argued that IABP-induced pulsatile flow may improve lung perfusion through the collateral bronchial circulation, in association with reduced vasoconstrictive reflexes, optimization of oxygen consumption, and reduced lung tissue acidosis.[20] Accordingly, this may explain the better results we observed in Group B patients in terms of P_aO_2/F_iO_2, RSC, SCR, intubation time and need for NIV.

Recent evidence showed that linear flows, during either CPB or left ventricular assistance, contribute to the systemic inflammatory response syndrome, which enhances the activation of the hemocoagulative cascade.[2,21] We found better preserved hematologic function (higher RBC and PLT, lower WBC, as a marker of lower neutrophil activation) in patients undergoing pulsatile flow. These data confirm Koster et al,[21] who found axial flow to strongly activate the coagulation and fibrinolytic systems. Following this, we found better preserved coagulative and fibrinolytic pathways (higher fibrinogen and AT-III, lower INR, aPTT, and D-dimer), suggesting a lower rate of consumption, in patients undergoing pulsatile perfusion. Moreover, different authors agree with our results,[2,22] showing lower coagulopathy, inflammation and need for transfusions when pulsatile flows are used. As a direct consequence of the lower inflammatory response, the higher PLT, the better coagulative and fibrinolytic pathways, patients in Group B required less transfusions of platelets and plasma.

When the hypothetical reduction of perfusion distal to IABP is considered, a nice in vitro model described by Kolyva et al showed that more than 40% of the blood flow from the aortic cannula is displaced downstream of the IABP.[22] However, although corresponding qualitative data are not available in vivo, published studies on the differences between non-pulsatile and IABP-induced pulsatile perfusion during CPB suggest the net effect of the IABP on the perfusion of different organs and vascular beds.[5–8,23] On the other hand, little is known about the pathophysiology; a recent study demonstrated that the maintenance of a steady pulsatile flow (in vitro) induces a steady shear stress on the endothelial cells, which remain in a "quiescent" state.[24] The modification of a pulsatile flow to a linear flow triggered endothelial cell activation, affecting environmental haemorrhagology, hemostasis, and inflammatory pathways.[25] It can be argued that the sequential translation from a pulsatile to a linear to a pulsatile state (corresponding to the pre-cross-clamping time, aortic cross-clamping, aortic de-clamping in cardiac surgery – in vivo), may imitate such an endothelial in vitro reaction, leading to different organ responses to CPB. Accordingly, the present study indicates less endothelial activation with pulsatile CPB, thus suggesting that the better clinical outcome of our previous studies can be ascribed to an attenuated endothelial response to CPB. In particular, VEGF and MCP-1 are considered biochemical markers of endothelial activation.[26,27] However, these chemokines have been poorly investigated in heart surgery. In the present study, when standard linear perfusion was used, a progressive rise in plasma MCP-1 was detected (peaking at ICU arrival) followed by a progressive fall, whereas when IABP-induced pulsatile perfusion was used, MCP-1 showed a slight fall at aortic de-clamping, thus suggesting a significant reduction of endothelial activation during cross-clamping, followed by a progressive increase in the subsequent time-course. Moreover, MCP-1 leakage proved to be significantly reduced during the entire postoperative period following IABP-induced pulsatile perfusion.

Generally, VEGF is an endothelial-derived growth factor with mitogen and vasorelaxing/vasodilating properties, both in vitro and in vivo.[27,28] Again, our study showed a significantly reduced VEGF secretion at aortic de-clamping and ICU arrival in pulsatile-CPB patients. Our data confirm those of Macha et al who demonstrated that non-pulsatile flow is associated with lowered endothelial shear stress and with a reduction in endothelial nitric oxide production, which may contribute to the detrimental physiologic effects observed with prolonged non-pulsatile flow.[12] Accordingly Orime et al found less endothelial damage and beneficial effects on the microcirculation with the pulsatile Jostra system,[14] as did Sezai et al, who demonstrated reduced endothelin-1 leakage and better peripheral circulation when pulsatile perfusion was used.[13]

Study Limitations

Despite the preoperative placement of IABP in high-risk coronary patients, which is the standard of care at our institution, this would not be the case in a significant number of other

institutions. However, we did report the results of the single-center design of the study itself, which, on the other hand, guarantees uniformity of the perioperative management of the patient population throughout the experimentation. Moreover, on an intention-to-treat basis, we enrolled patients with the most similar risk profile, avoiding severe organ comorbidities, which may give misleading results. One other limitation of the study is the lack of hemodynamic measurements distal to the IABP. Accordingly, further studies on this topic with different modalities of CPB, perioperative care and subsets of patients are welcome to better define the role of pulsatility in organ response and endothelial activation during cardiac operations.

We conclude, therefore, that IABP-induced pulsatile perfusion achieves a better multi-organ response to CPB in CABG patients. The use of IABP in automatic mode during cross-clamping does not add further risk to patients undergoing preoperative IABP, but significantly improves whole-body perfusion, endothelial protection and organ function.

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