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Impact of cardiac surgery with cardiopulmonary bypass on symptom progression in the early postoperative period in patients with peripheral arterial disease

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Abstract. – OBJECTIVE: This study aims to examine whether cardiac surgery with cardiopulmonary bypass (CPB) leads to symptom progression in the early postoperative period in patients with the peripheral arterial disease (PAD) undergoing coronary artery bypass grafting surgery (CABG).

PATIENTS AND METHODS: This retrospective study included one hundred fifty consecutive adult patients with PAD at Fontaine stage 2b (pain-free walking distance less than 100 m) undergoing CABG. The control group comprised 150 consecutive adult patients undergoing CABG with a normal ankle-brachial index (ABI). Symptom progression was defined as the development of ischemic rest pain (Fontaine stage 3).

RESULTS: In the first week after surgery, 91 of 150 patients (60.6%) had symptom progression in the PAD group. Rest pain resolved in most of these patients on the 15th postoperative day. At the end of the second month, rest pain resolved in all patients. Logistic regression analysis revealed that ABI (<0.5), CPB time (≥100 mins), nadir hct levels (≤25 %) on CPB, and postoperative nadir hct levels (<25%) were independently associated with postoperative symptom progression.

CONCLUSIONS: Our results suggest that cardiac surgery with CPB may lead to symptom progression in patients with severe claudication in the early postoperative period.

Key Words:
Cardiopulmonary bypass, Coronary artery bypass, Peripheral arterial disease, Symptom progression, Cardiac surgery.

Introduction

Cardiopulmonary bypass (CPB) is commonly used to secure adequate systemic oxygenation and perfusion during cardiac surgical procedures[1]. The primary objectives of CPB are to provide hemodynamic stability and maintain myocardial and systemic tissue oxygenation. Oxygen delivery (DO_2) during CPB is dependent on the pump flow rate and arterial oxygen content. Hemodilution is a standard practice during CPB. Even if the global DO_2 and pump flow are adequate, excessive hemodilution and the resulting anemia during CPB are accompanied by a decrease in the total arterial oxygen content, impairing tissue DO_2 and leading to organ dysfunction after cardiac surgery[1]. Studies have shown that transfusion of red blood cells fails to improve tissue oxygenation. Because of the changes in stored red blood cells, packed red blood cells appear to have a significantly limited capacity to deliver oxygen to tissues acutely[2]. Furthermore, CPB was reported to cause reduced microvascular perfusion and tissue DO_2 leading to tissue hypoxia[3].

Peripheral arterial disease (PAD) is common in coronary artery disease (CAD) patients, with 22-42%[4,5]. Diminished arterial flow may lead to tissue hypoxia in patients with PAD. Cardiac surgery with CPB may further exacerbate tissue hypoxia in patients with PAD. It is unclear whether cardiac surgery with CPB leads to symptom progression in PAD patients.

This study examines whether cardiac surgery with CPB leads to symptom progression in the early postoperative period in patients with PAD undergoing coronary artery bypass grafting surgery (CABG). To our knowledge, no study has been conducted to investigate this issue.

Patients and Methods

Study Population and Design

We retrospectively reviewed the medical records of adult patients who underwent CABG

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between January 2011 and December 2018. The study included one hundred fifty consecutive adult patients with PAD at Fontaine stage 2b (pain-free walking distance less than 100 m) undergoing CABG. The control group comprised 150 consecutive adult patients undergoing CABG with a normal ankle-brachial index (ABI).

Exclusion criteria were as follows: patients who underwent emergent or salvage surgery, patients who had dialysis-dependent renal failure, patients who suffered low cardiac output syndrome in the perioperative period, patients who required vasoconstrictive agents in the perioperative period, patients with hypoxemia in the perioperative period, patients with mild and moderate claudication and ischemic rest pain. Since the walking test cannot be applied in patients with coronary artery disease in the preoperative and early postoperative period, patients with mild and moderate claudication were not included. In the early postoperative period, it is impossible to determine symptom progression in patients with mild and moderate claudication and ischemic rest pain. The preoperative clinical characteristics of the patients are summarized in Table I. This study was approved by our Local Ethics Committee (University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee) and complied with the requirements of the Declaration of Helsinki (Ethical Approval Number 159).

Operative Details

All procedures were performed using a standard general anesthesia protocol. Procedures were performed with median sternotomy. Standard non-pulsatile CPB with a roller pump and a membrane oxygenator was used. The extracorporeal system was primed with the ringer`s lactate solution. CPB was established using bicaval cannulation and ascending aorta cannulation. Before cannulation, 300-400 U/kg heparin sodium was administered, and activated clotting time values were maintained above 480 s. During CPB, non-pulsatile pump flow was kept at 2.2-2.5 L/min/m^2. The core temperature was cooled to 28°C. The alpha-stat strategy was used for pH management, and all patients were kept at normocapnic levels ($PaCO_2$=35-45 mmHg). Concentrated fresh erythrocyte suspensions ($\leq$ 7 days of storage) were added to the pump-priming volume if required to keep the hematocrit levels above 25% during CPB. The mean arterial pressure was stabilized between 50 mmHg and 70 mmHg during CPB. In all patients, hematocrit levels were kept above 25% in the postoperative period.

Graft Harvesting

The great saphenous vein was harvested from the leg without PAD via an open harvest technique. If both legs had PAD, the saphenous vein was harvested starting from the thigh. In the case of iliac artery occlusion, the ipsilateral internal mammarian artery was not harvested to maintain the collateral pathway between the internal mammarian artery and the inferior epigastric artery.

Evaluation of Symptom Progression

The severity of PAD was determined using the Fontaine classification[6]. Since it is impossible to perform a walking test in patients with coronary artery disease during the perioperative period, an evaluation for pain-free walking distance was not performed. The patient's self-reported walking data was used to determine the severity of PAD.

Symptom progression was defined as the development of ischemic rest pain (Fontaine stage 3). Patients were evaluated for symptom progression in the first week after surgery, fifteen days after surgery, and two months after surgery. Patient statements were taken into consideration. All patients who had symptom progression in the postoperative period were evaluated with colour doppler ultrasound.

Blood Samples

Blood gas analyses were performed at the following time points: after the induction of anesthesia, before CPB, during CPB (at 30-min intervals), before separation from CPB, after CPB termination, and at the end of the surgery, and every 4 hours until discharge from the ICU. The blood samples for measuring central venous oxygen saturation ($ScVO_2$) were collected from the central venous catheter inserted in the right internal jugular vein. Blood gas analyses and lactate levels were assessed via an automated analyser.

Tissue Oxygenation

$ScVO_2$ and serum lactate levels were used as an index of tissue oxygenation. Tissue hypoxia was defined as hyperlactatemia (lactate >2.2 mmol/L) coupled with low $ScVO_2$ ($ScVO_2$ <70%) during CPB. $ScVO_2$ and lactate values were collected retrospectively by chart review.

Statistical Analysis

Statistical analysis was conducted using SPSS for Windows version 26 (IBM Corp. Armonk, NY,

Table I. Baseline characteristics and comorbidities.

	PAD (n=150)	Control (n=150)	*p-value*
Age, years, mean±SD	62.3 ± 11.2	60.1 ± 10.3	0.08
Male, n (%)	115 (76.7)	86 (57.3)	<0.001
Smoking, n (%)	99 (58.9)	69 (41.1)	<0.001
HT, n (%)	78 (52)	64 (42.7)	0.1
HL, n (%)	93 (62)	65 (43.3)	0.001
DM, n (%)	64 (42.7)	38 (25.3)	0.002
COPD, n (%)	49 (32.7)	46 (30.7)	0.71
Carotid Stenosis, n (%)	16 (10.7)	5 (3.3)	0.01
History of CVE, n (%)	14 (9.3)	5 (3.3)	0.03
Renal dysfunction, n (%)	11 (7.3)	3 (2)	0.03
EF, mean±SD	50.7 ± 6.2	51.9 ± 5	0.06
AF, n (%)	11 (7.3)	6 (4)	0.21
ABI, median (IQR)	0.49 (0.44-0.53)		
Location of the arterial disease, n (%)			
Iliac arteries	26 (17.3)		
Common Femoral artery	58 (38.6)		
Superficial femoral artery	14 (9.3)		
Popliteal artery	13 (8.6)		
Below the knee popliteal artery	39 (26)		

Values are presented as mean ± standard deviation, median (interquartile range), or n(%). p <0.05 was considered statistically significant.
PAD: peripheral arterial disease; HT: Hypertension; HL: Hyperlipidemia; DM: Diabetes mellitus; COPD: chronic obstructive pulmonary disease; CVE: Cerebrovascular event; EF: Ejection Fraction; AF: atrial fibrillation; ABI: ankle brachial index.

USA). To determine whether they were normally distributed, all variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov-Smirnov test). Continuous variables were reported as means and standard deviation for normally distributed variables and as medians and interquartile range (IQR) for non-normally distributed variables. Categorical variables were presented using numbers and percentages. Comparison between the two groups was performed using the Chi-squared test for qualitative variables, the independent *t*-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. Logistic regression analysis was performed to determine the variables associated with symptom progression. Postoperative symptom progression was used as the dependent variable. Potential risk factors for postoperative symptom progression and possible predictor variables with a *p*-value less than 0.25 in the univariate analysis were identified and included as covariates in the multivariate model. *p*-values less than 0.05 were considered to indicate statistical significance.

Results

A total of 300 patients were enrolled in this study (201 males; mean age 61.2 ± 10.8).

Univariate Analysis

Table I presents the clinical and biochemical characteristics of patients with PAD (n=150; 114 males, mean age 62.3 ± 11.2) and the control group (n=150; 86 males, mean age 60.1 ± 10.3).

The percentage of males was significantly higher in the PAD group. PAD group had a significantly higher rate of diabetes mellitus (p=0.002), hyperlipidemia (p=0.001), carotid stenosis (p=0.01), history of cerebrovascular events (p=0.03), renal dysfunction (p=0.03) and smoking (p<0.001). No other statistically significant differences were observed between the two groups in clinical characteristics.

Table II presents the operative and postoperative characteristics of the patients with PAD and the control group. Patients in the PAD group had a significantly higher anastomosis (p<0.001). Compared with the control group, patients with PAD were associated with significantly higher lactate levels and lower $ScVO_2$ during CPB (p<0.005 and p<0.001, respectively). Patients with PAD had a significantly higher tissue hypoxia incidence than patients in the control group (p<0.001). Postoperative peak creatine kinase (CK) levels were significantly higher in the PAD group (p<0.001). 91 of 150 patients (60.6%) had symptom progression in the PAD group. On postoperative day 15, 39 (26%) patients in the PAD group had persistent

Table II. Operative characteristics of the patients according to presence or absence PAD.

	PAD (n=150)	Control group (n=150)	*p-value*
Anastomoses, mean±SD	4.01 ± 0.98	3.57 ± 1.11	<0.001
CPB time, min, median (IQR)	119 (95-137)	119.5 (81.7-135)	0.11
ACC time, min, mean±SD	77.3 ± 23.2	74.9 ± 28.34	0.45
Nadir HCT on CPB, mean±SD	24.54 ± 3.7	24.53 ± 2.6	0.98
$ScVO_2$, %, median (IQR)	68 (63-71.2)	71 (68-72)	<0.001
Peak lactate during CPB, mmol/L, median (IQR)	2.6 (2-3.2)	2 (1.9-2.3)	<0.001
Tissue hypoxia, n(%)	79 (52.7)	27 (18)	<0.001
Postoperative peak CK, IU/L, median (IQR)	1542 (1150-1957.5)	766 (605-989)	<0.001
Postoperative symptom progression, n (%)		-	
- within the first week after the surgery	91 (60.6)	-	
- at 2 weeks follow-up	39 (26)	-	
- at 2 months follow-up	-	-	
Postoperative peak lactate, mmol/L, median (IQR)	2.2 (1.9-2.62)	2 (1.8-2.12)	<0.001
Number of transfusions, mean±SD	1.7 ± 0.56	1.7 ± 0.61	0.29

Values are presented as mean ± standard deviation, median (interquartile range), or n(%). p <0.05 was considered statistically significant.
PAD: peripheral arterial disease; HT: Hypertension; HL: Hyperlipidemia; DM: Diabetes mellitus; COPD: chronic obstructive pulmonary disease; CVE: Cerebrovascular event; EF: Ejection Fraction; AF: atrial fibrillation; ABI: ankle brachial index.

symptoms. By the end of the two months, none of the patients had ischemic rest pain. No new cases were seen after the first week following surgery. There were no other statistically significant differences between the two groups in operative and postoperative characteristics.

According to symptom progression after cardiac surgery, the patients in the PAD group were divided into two subgroups. Table III presents the clinical characteristics of the patients in each subgroup. The patients with symptom progression were associated with significantly higher rates of diabetes mellitus (p=0.006), lower ABI (p<0.001), a higher number of anastomoses (p<0.001), higher CPB and aortic cross-clamp times (p<0.001 and p<0.001, respectively), lower nadir hematocrit levels (HCT) on CPB (p<0.001), higher intraoperative lactate levels (p<0.001), higher postoperative lactate levels (p<0.001), lower postoperative nadir hct levels (p<0.001) and higher postoperative peak CK levels (p<0.001). Patients with symptom progression had higher intraoperative and postoperative tissue hypoxia incidence (p=0.02 and p=0.002, respectively). None of the patients in the symptom progression group required intervention. No other statistically significant differences were observed between the two groups in clinical characteristics.

Multivariate Analysis

Table IV presents the results of the logistic regression analysis. After adjusting for age, gender, diabetes mellitus, smoking, intraoperative tissue hypoxia and postoperative tissue hypoxia, logistic regression analysis revealed that ABI (<0.5) (OR: 4.6; 95% CI: 1.8-11.3; p=0.001), CPB time (≥100 mins) (OR: 7.2; 95% CI:2.6-20.3; p<0.001), nadir hct levels (≤25%) on CPB (OR: 4.6; 95% CI:1.4-15.2; p=0.01), and postoperative nadir hct levels (<25%) (OR: 3.4; 95% CI: 1.09-10.8; p=0.03) were independently associated with postoperative symptom progression.

Discussion

These results reveal that cardiac surgery with CPB leads to symptom progression in patients with severe claudication in the first week after surgery. Most patients improved by 2 weeks follow-up, and those who had not improved within 2 months. They also indicate that an ABI <0.5, CPB time (≥100 mins), nadir hct levels ≤25% during CPB, and postoperative nadir hct levels <25% were independent risk factors for symptom progression in patients with PAD undergoing CABG with CPB. There were no ischemic symptoms in the control group. To our knowledge, this is the first study exploring the symptom progression after cardiac surgery with CPB in patients with PAD.

Various pathways may be responsible for symptom progression, generally involving decreased oxygenation of tissues. The delivery of oxygen to the tissues is equally dependent on the blood flow and the O_2 content of the blood. CPB

Table III. Differences in clinical and biochemical characteristics of the patients with peripheral arterial disease according to the presence or absence of symptom progression.

	No SP (n=59)	SP (n=91)	*p-value*
Age, years, mean±SD	64.8 ± 11.4	60.7 ± 10.8	0.03
Gender, male, n (%)	42 (71.2)	73 (80.2)	0.2
BMI, kg/m², mean±SD	24.1 ± 2.9	23.7 ± 3.2	0.46
HT, n (%)	32 (54.2)	46 (50.5)	0.66
HL, n (%)	31 (52.5)	62 (68.1)	0.055
Smoking, n (%)	41 (69.5)	58 (63.7)	0.47
DM, n (%)	17 (28.8)	47 (51.6)	0.006
COPD, n (%)	18 (30.5)	31 (34.1)	0.65
ABI	0.52 ± 0.05	0.46 ± 0.06	<0.001
Anastomoses, median (IQR)	3 (3-4)	5 (4-5)	<0.001
CPB time, min, median (IQR)	95 (85-120)	131 (102-142)	<0.001
ACC time, min, median (IQR)	56 (47-78)	89 (72-103)	<0.001
Nadir hct on CPB, median (IQR)	26 (25-28)	23 (20-26)	<0.001
$ScVO_2$, %, median (IQR)	69 (63-72)	68 (64-70)	0.5
Intraoperative lactate, mmol/L, median (IQR)	2.15 (1.9-2.8)	2.8 (2.3-3.3)	<0.001
Intraoperative Tissue hypoxia, n (%)	24 (40.7)	55 (60.4)	0.02
Postoperative peak CK, IU/L, median (IQR)	1275 (917-549)	1741 (1387-2112)	<0.001
Postoperative nadir hct levels, median (IQR)	25 (25-26)	24 (23-25)	<0.001
Postoperative peak lactate levels, mmol/L, median (IQR)	2 (1.8-2.2)	2.4 (2-2.7)	<0.001
Postoperative $SCVO_2$, %, mean±SD	71 ± 2.8	70.9 ± 2.04	0.79
Postoperative tissue hypoxia, n (%)	1 (1.7)	11 (12.1)	0.02
Need for arterial intervention,n(%)	-	-	
Location of the greatest stenosis, n (%)			
Iliac arteries	12 (13.2)	14 (23.7)	
Common Femoral artery	32 (35.1)	26 (44)	
Superficial femoral artery	10 (11)	4 (6.8)	
Popliteal artery	8 (8.8)	5 (8.6)	
Below the knee popliteal artery	29 (31.9)	10(16.9)	

Values are presented as mean ± standard deviation, median (interquartile range), or n (%). $p<0.05$ was considered statistically significant.
SP: Symptom progression; BMI: Body mass index; HT: Hypertension; HL: Hyperlipidemia; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; ABI: ankle brachial index; CPB: Cardiopulmonary bpass; ACC: Aortic cross clamp; Hct: Hematocrit levels; $ScVO_2$: Central venous oxygen saturation; CK: Creatine kinase.

may lead to reduced whole-body DO_2[1]. Hemodilutional anemia is inevitable during CPB and may decrease tissue DO_2[1]. Blood transfusion augments systemic DO_2 but may not improve oxygenation at the tissue level and may further deteriorate the ischemic organ injury[2,7].

In addition, perfusion of microcirculation should be sufficient to preserve tissue oxygenation. Earlier studies have shown that surgical trauma, anesthesia, microemboli formation, hypothermia, hemodilution, endothelial dysfunction, and the systemic inflammatory response may result in decreased capillary density and microvascular flow and reduced organ perfusion following cardiac surgery with non-pulsatile CPB[3,8]. The microcirculatory disturbances were reported to lead to acute organ dysfunction, increased morbidity, and mortality in the ICU in cardiogenic shock or sepsis patients[3,9]. Under normal conditions, microcirculatory tissue perfusion is largely homogenous. Microcirculatory heterogeneity of flow leads to impaired tissue oxygen extraction[3,8] and is associated with unfavourable outcomes in multiple patient populations[9-11]. Several mechanisms have been suggested for reduced microcirculatory perfusion[1,3,9-11]. Systemic inflammation and activation of complement and coagulation lead to shedding of the endothelial protective glycocalyx layer, causing endothelial injury. In addition, the release of barrier disruptive mediators induces endothelial barrier disruptive signalling, resulting in capillary leakage and edema formation. Activation of the endothelium stimulates the release of nitric oxide, affecting vascular tone and systemic blood pressure. Reduced shear stress on the luminal side of the endothelium secondary to non-pulsatile flow causes diminished endothelial nitric oxide synthase activity and increased endothelin-1

Table IV. Results of the logistic regression analysis.

	OR	95% CI	*p-value*
Age	0.97	0.93-1.01	0.18
Female Gender	1.8	0.6-5.5	0.28
DM	1.7	0.6-4.4	0.27
Smoking	0.51	0.2-1.3	0.17
ABI (<0.5)	4.6	1.8-11.3	0.001
CPB time (≥100 mins)	7.2	2.6-20.3	<0.001
Nadir Hct on CPB (≤25 %)	4.6	1.4-15.2	0.01
Postoperative nadir Hct (<25%)	3.4	1.09-10.8	0.03
Intraoperative Tissue hypoxia	1.5	0.6-3.8	0.36
Postoperative Tissue Hypoxia	5	0.5-54.3	0.19

DM: Diabetes mellitus; ABI: Ankle brachial index; CPB: Cardiopulmonary bypass; HCT: Hematocrit levels; OR: Odds ratio; CI: Confidence interval.

production, leading to increased prothrombogenicity arteriolar vasoconstriction[1,3,9-11]. In addition, leucocyte rolling and extravasation are increased due to endothelial adhesion molecule expression induction. Moreover, reactive oxygen species are released from the activated polymorphonuclear neutrophils, increasing tissue injury. Furthermore, the coagulation system and platelets are activated, leading to microthrombi and microvascular occlusion. Together, these mechanisms reduce microcirculatory perfusion and contribute to organ injury following cardiac surgery with CPB[1,3,9-11]. Heterogeneous perfusion of the microcirculation consists of capillaries with low blood flow and capillaries with extremely high blood velocities. Hyperdynamic vessels cause inefficient red blood cell offloading and thus lead to a functional arteriovenous shunt of oxyhemoglobin. As a result of reduced microvascular perfusion, local tissue hypoxia occurs even though overall global DO_2 is maintained and macrocirculatory variables are adequate[1,3,9-11]. Impairment of microvascular perfusion and resultant local tissue hypoxia was associated with organ dysfunction and worse patient outcomes[12,13]. Although hemodilution contributes to altered microcirculatory flow patterns, decreased microcirculatory perfusion during bypass is substantially caused by systemic inflammation. Thus, correcting hematocrit levels alone may not sufficiently restore microcirculatory oxygen delivery and extraction[3,7,10]. The duration of reduced microvascular impairment remains unclear. Microcirculatory perfusion disturbances were reported to persist for the first three postoperative days, despite restoration of temperature and hematocrit[10]. Kim et al[14] and Scolletta et al[15] demonstrated that microcirculatory perfusion disturbances continued for longer in those with complications. In our study group, it was observed that some patients' complaints continued by the end of the second week. This may be due to decreased HCT levels rather than microvascular perfusion disturbances. Opposite results were also found in the previous studies. Maier et al[16] reported that CPB did not impair microcirculatory perfusion. At the same time, an additional phenylephrine-induced systemic blood pressure increases reduced small vessel blood flow and augmented tissue hemoglobin oxygenation[16]. Other studies demonstrated that microvascular perfusion was almost expected at 30 minutes following cardiac surgery[17].

In addition to microcirculatory alterations and hemodilution, factors such as anesthesia, low cardiac output state, the administration of sedative or vasopressor agents, a residual neuromuscular blockade in the first postoperative hours, and variations in body temperature may affect O_2 extraction and consumption in skeletal muscle[8,18]. Moreover, vasopressors, inotropes, transfusions, mechanical ventilation, body temperature, acid-base balance, and perioperative fluid balance could affect peripheral tissue oxygen supply and utilisation[8,15,18,19].

Factors such as anesthesia, type of surgery (off-pump *vs.* on-pump), and type of blood flow (pulsatile *vs.* nonpulsatile) during CPB may influence the effect of cardiac surgery on sublingual microcirculatory perfusion[3,17,19-21].

In patients without PAD, muscle tissue has a low resting metabolic rate and has a high tolerance to ischemia[11,22]. PAD presents as inadequate tissue perfusion due to atherosclerosis. Delivery of oxygen to tissues is reduced in these patients. Thus, PAD patients are known to be unable to compensate for anemia and blood loss, which leads to a further reduction in DO_2. Anemia resulting from

hemodilution and reduced microvascular perfusion during CPB and in the postoperative period can further exacerbate the imbalance between oxygen supply and demand in PAD patients[23,24]. It is difficult to determine the lowest hemoglobin concentration that does not result in increased anaerobic metabolism. The critical hemoglobin concentration varies among individuals. DO_2 is already reduced in patients with PAD. Thus, even a slight decrease in hemoglobin levels can lead to symptom progression in PAD patients[23,24].

The effect of CPB on muscle perfusion was examined in the earlier studies[8,22]. Findings of these studies indicated that CPB disrupted peripheral tissue (skeletal muscle) energy metabolism, and skeletal muscle metabolism was shifted toward more anaerobic metabolism earlier after surgery. Furthermore, they found that increased anaerobic metabolism was caused by reduced DO_2 and not reduced oxygen extraction ability in skeletal muscle. Although it was claimed that these changes had no impact on the postoperative clinical outcome, these studies did not involve patients with PAD.

Moreover, cardiac output redistribution may occur during cardiac surgical procedures, causing peripheral tissue vasoconstriction and hypoperfusion. The CPB-produced blood flow is distributed due to an organ hierarchy. The brain has the highest priority, and the muscle tissue has the lowest priority[25]. Centralization of the circulation may further exacerbate muscle hypoxia and contribute to symptom progression in patients with PAD[11].

Although hypothermia, controlled hemodilution, and the decrease of blood pressure with constant cardiac output reduce the energy requirement of the cells, these factors may result in the activation of the adrenergic system with consequent deterioration of the vasoconstriction of the peripheral and splanchnic vessels. These changes may lead to severe renal, gastrointestinal, or hepatopancreatic complications or ischemia of extremities, mainly if the arteries are affected before surgery[11]. Hypothermia decreases the basal oxygen demand during CPB; on the other hand, the neurohumoral stress and the systemic inflammatory response cause trauma metabolism, which increases basal oxygen demand. This is characterized by increases in lipolysis and circulating free fatty acids (FFA) levels leading to insulin resistance. FFA oxidation consumes 12% more oxygen than carbohydrates to produce the same amount of ATP[25]. Previous studies have also shown that anesthetic agents significantly affect microcirculation. Microvascular reactivity can be affected positively and negatively[19].

The above mechanisms may have contributed to symptom progression observed in our study. In our study, it was found that an ABI <0.5, CPB time (≥100 mins), nadir hct levels ≤25% during CPB, and postoperative nadir hct levels <25% were independent risk factors for symptom progression. Thus, reduced blood flow and reduced hematocrit levels, and resultant tissue hypoxia and reduced microcirculatory perfusion may explain symptom progression after CPB. Our study design precludes us from stating if one factor is more responsible than another for the symptom progression in PAD patients.

Limitations

This study had several limitations. First, our study had a retrospective design. Second, it was conducted in low-risk patients without hemodynamic instability. Therefore, the results of this study might not be extrapolated to high-risk patients or patients who have perioperative low cardiac output syndrome. Additionally, we examined the influence of cardiac surgery with CPB on symptom progression in patients with Fontaine stage 2b symptoms. Further studies are needed to assess the effects of cardiac surgery with CPB in patients with mild to moderate claudication and more severe symptoms. Finally, symptom progression was defined as the development of ischemic rest pain. The walking test cannot be applied to determine the decrease in pain-free walking distance in the perioperative period. Thus, the rate of symptom progression may be underestimated.

Conclusions

Our results suggest that cardiac surgery with CPB may lead to symptom progression in patients with severe claudication in the early postoperative period. None of the patients in the symptom progression group required vascular intervention, and in all patients, symptoms resolved within two months. Nevertheless, our results may not be generalizable to patients with mild to moderate claudication and more severe symptoms. Further investigations should be performed to clarify the effects of cardiac surgery with CPB in patients with mild to moderate claudication and more severe symptoms.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Ethical Approval

This study was approved by our Local Ethics Committee (University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee) and complied with the requirements of the Declaration of Helsinki (Ethical Approval Number 159).

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