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Effects of atorvastatin on arterial endothelial function in coronary bypass surgery

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Abstract

Objective: Endothelial dysfunction represents a critical early component of organ injury following cardiopulmonary bypass. Recent studies demonstrate that the treatment with atorvastatin is associated with a significant improvement of endothelial function independently of its efficacy on cholesterol levels. Therefore, we investigated the effects of preoperative atorvastatin treatment on endothelium function after coronary surgery. **Methods:** Forty patients undergoing coronary surgery were randomized to treatment with atorvastatin (20 mg/die; $N = 20$) or placebo ($N = 20$) 3 weeks before surgery. Twenty normal patients served as control group. The flow-mediated dilations (FMD) of the brachial artery after both reactive hyperemia (endothelium dependent) and nitroglycerin administration (endothelium independent) were evaluated at baseline, at 48 h, and 5 days postoperatively. **Results:** At baseline, the endothelium-dependent FMD was significantly attenuated in coronary versus normal patients (normal $10.3 \pm 1.8\%$ vs coronary $4.1 \pm 1.6\%$, $p < 0.01$). At 48 h postoperatively all patients exhibited a reduced FMD compared with baseline values: the endothelium-dependent dilatation showed a drop of 60.1 + 15% in the patients of the placebo group compared with 45.8 + 16.6% ($p < 0.05$) those in the atorvastatin group. At the univariate analysis, no significant correlation was found between serum levels of either total cholesterol or HDL cholesterol and FMD. The nitroglycerin-induced dilation was not significantly influenced by extracorporeal circulation as well as by atorvastatin treatment. **Conclusions:** The endothelial dysfunction following cardiopulmonary bypass is improved by the treatment with atorvastatin, by a mechanism unrelated to the drug efficacy of controlling serum cholesterol levels.

Keywords: Atorvastatin; Endothelium; Cardiopulmonary bypass

1. Introduction

The normal endothelium plays a key role in the local regulation of the vascular tone by producing and releasing contracting and relaxing agents [1]. One of these factors is the nitric oxide (NO) [2] that is released after stimulation of endothelial cells by shear stress, as well as some agonists such as acetylcholine (Ach), bradykinin, substance P, and serotonin. On the other hand, nitroglycerin (NTG) is an endothelium-independent vasodilator compound that produces vasodilation by direct activation of guanylate cyclase in vascular smooth-muscle cells by providing inorganic source of NO [3]. Endothelial dysfunction has long been shown to be a critical early component of organ injury following cardiopulmonary bypass (CPB) [4,5], and various factors have been identified as potential determinants, including the hypoxia during cardioplegic arrest, the inflammatory effects of cytokines and endotoxins, as well as direct physical damage [6]. All these insults produce a rapid alteration of cellular phenotype that is characterized by loss of the ability to synthesize and release NO [7]. Therefore, a dysfunctioning endothelium reduces its ability to exert a protective effect on the vascular system and increase the risk of postoperative complications [8].

The 3-hydroxy-3-methyl-glutaryl coenzyme-A (HMG-CoA) reductase inhibitors, simply known as ''statins'', are substances widely employed in the control of hypercholesterolemia. Clinical trials have shown that statins notably reduce cardiovascular morbidity and mortality in subjects with and without established coronary artery disease, and improve cardiovascular outcome after coronary artery bypass grafting [9—11]. Moreover, recent studies demonstrate that the treatment with atorvastatin is associated with a significant improvement of blood flow in the forearm after reactive hyperemia [12,13] and after intra-arterial administration of acetylcholine [14]. However, at present no data

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are available about the atorvastatin effects on endothelial dysfunction following cardiopulmonary bypass. Based on these observations, the aim of this study was to test the effect of atorvastatin on endothelial function in patients undergoing coronary bypass surgery with CPB.

2. Study protocol

From May 2003 to September 2004, patients scheduled to undergo elective coronary artery bypass graft (CABG) surgery at our center were evaluated. Diabetic patients and patients with renal or hepatic impairment, congestive heart failure, active inflammatory or immunomodulatory diseases, a history of myocardial infarction in the past 6 months, pregnant women, and those with nitrate administration in the 24 h preceding first testing were excluded. Forty subjects who fulfilled the inclusion criteria were randomized to treatment with atorvastatin (20 mg/die; group A, $N = 20$) or placebo (group B, $N = 20$) 3 weeks before surgery. A recent study indicates that many short-term pleiotropic effects of atorvastatin therapy occur within 2 weeks, which may be important with respect to the early benefits of statin therapy [10]. Both patients and physicians were blinded to the drug assignment group. The patients had not taken any other cholesterol lowering drugs for at least a year. Twenty normal volunteers, 15 men and 5 women, aged 32–65 years (mean 52.2 years), were selected as a normal group. Each patient in this group underwent clinical history, physical examination, standard electrocardiogram, routine chemical analyses, and chest X-rays. None had evidence of present or past hypertension, cardiovascular disease, hyperlipidemia, or any other systemic condition and none was taking drugs at the time of the study. The study protocol was approved by the local ethics committee. Informed consent was obtained from each patient.

2.1. Operative procedure and postoperative care

All patient underwent coronary bypass surgery with CPB using standard procedures. Induction and maintenance of anesthesia were similar for all patients and consisted of weight-related doses of fentanyl, midazolam, and pancuronium bromide. After premedication, a Swan–Ganz catheter was positioned in the central pulmonary artery and a radial artery cannula was inserted. The pump (Sarns roller pumps, Ann Arbor, MI, USA and hollow fibers oxygenators, Dideco, Mirandola, Italy) was primed with 1500 ml of Ringer's lactate plus 200 ml of 20% mannitol. The heart was exposed through a median sternotomy, and 300 U/kg of sodium heparin was administered intravenously before CPB to produce an activated clotting time of greater than 400 s. The hematocrit value was maintained between 20% and 25%, and pump flows were kept between 2.0 and 2.5 l min^{-1} m^{-2} to keep the mean arterial pressure between 50 and 70 mmHg. All patients were cooled to moderate hypothermia (mean 32 °C), and cardioplegic arrest was achieved with cold blood cardioplegia (4 °C) infused into the ascending aorta. The left ventricle was vented through the aortic root. After decannulation, protamine sulfate (10 mg/ml, Lilly, Indianapolis, IN, USA) was administered intravenously at a dose of 1 mg/300 units of heparin to neutralize the heparin.

At the end of surgery, patients were transferred to the Intensive Care Unit (ICU). The lungs were ventilated with 60% oxygen using volume-controlled ventilation (Servo Ventilator 900C; Siemens, Stockholm, Sweden) and a tidal volume of 10 ml/kg with 5 cmH_2O of PEEP. Arterial blood gas analysis was determined by standard techniques using automated analyzer at anesthesia induction at 4-h interval for 24 h after termination of CPB. All patients were extubated in the Intensive Care Unit when Tobin Index (respiratory rate (spontaneous)/tidal volume (l)) was less than 105, PaO_2 was higher than 60 mmHg with FiO_2 less than 0.4, CPAP less than 5 mbar, $PaCO_2$ less than 50 mmHg and arterial pH higher than 7.35.

3. Assessment of the endothelial function

The endothelial function was assessed by the ultrasonic measurement of flow-mediated vasodilatation (FMD) in the brachial artery, a method that is strongly correlated with coronary endothelial function [15]. All patients had three successive peripheral endothelial function studies: at 24–36 h preoperatively, at 48 h postoperatively, and at 5 days postoperatively. All studies were performed at 9:00 a.m. after overnight fasting, with the subjects lying supine in a quiet air-conditioned room (22–24 °C), using the same protocol previously described by Morelos and coworkers [5]. All vasoactive drugs were interrupted at least 24 h before the measurements. In three patients of statin group and in two of placebo group A, Ca^{2+} channel blockers infusion (diltiazem 5 mg/h) have been continued until 12 h before the first postoperative analysis.

The diameter of the brachial artery was measured from two-dimensional ultrasound images using a commercially available system (ESAOTE Megas GPX, 7.5-MHz probe). In each study, scans were taken at rest, during reactive hyperemia, at rest again, and after sublingual nitrates. The brachial artery on the dominant arm was scanned in longitudinal section, 3–7 cm above the antecubital crease. The arterial diameter was measured from anterior to posterior "m" line at end-diastole (R wave on the electrocardiogram) at a fixed distance from an anatomic marker, such as a bifurcation. Five cardiac cycles were analyzed and averaged for each scan. Following the baseline measurements, a blood pressure cuff was inflated on the proximal portion of the arm to 250–300 mmHg and occlusion was maintained for 4.5 min. Artery diameter was measured 1 min after cuff deflation. The flow-mediated dilator response was used as a measure of endothelial-dependent vasodilation.

After 10 min of vessel recovery, a resting scan was repeated. Sublingual nitrates (0.4 mg) were then administered to evaluate endothelium-independent vasodilatation (NMD). The last set of scans was performed 3 min after nitrate intake. All the studies were performed by two operators blinded to the patient assignment group. FMD is expressed as a percentage change of the brachial artery diameter (vasodilatation), which was determined by dividing the difference from baseline diameter (mean of three baselines) by the baseline value. A FMD $> 5\%$ was considered as normal.

Twenty randomly selected images were reanalyzed to assess intra-observer variation; the variations for FMD and NMD were, respectively, 1.4 ± 1% and 1.9 ± 1.5% (coefficient of variation 5% and 7%, respectively).

4. Statistical analysis

Standard descriptive and comparative analyses were undertaken. Data are presented as mean (SD). Mann–Whitney *U*-test or analysis of variance (ANOVA) as appropriate were used for comparing mean values of selected variables in the subjects under examination. Proportions were compared by χ^2-test or Fisher's exact test when appropriate. The following parameters were evaluated first in a univariate model: FMD, NMD, age, gender, clinical pattern, body mass index, brachial artery diameter, systemic hypertension, total cholesterol and HDL cholesterol, cigarette smoking, CPB time, and statin therapy group. Variables with a probability value <0.15 were then entered into a multivariate logistic regression analysis. A p value <0.05 was considered significant. All statistical analyses were performed using SPSSC version 4.0.1 (SPSS Inc., Chicago, IL, USA).

5. Patients

Clinical and operative characteristics are shown in Table 1. Compared with the normal patients, the coronary patients were older, with an higher prevalence of risk factors for coronary artery disease, particularly hyper-triglyceridemia, smoke, and hypercholesterolemia. The two treatment groups were considered comparable with respect to preoperative issues. All patients had angina on effort and were receiving some combination of β-adrenergic blocking agents, nitrate vasodilators, and calcium channel blocking agents. No patient in both groups was receiving corticosteroids or other non-steroidal anti-inflammatory drugs. All patients randomized for atorvastatin treatment did not experienced any side effect related to the drug. Patients were similar with regard to type of procedures, bypass time, and aortic clamping time. Compared with the pre-treatment values, in the statin group the preoperative lipid profile was beneficially affected by treatment (total cholesterol: 5.4 ± 0.6 nmol/l vs 6.2 ± 1 nmol/l, $p = 0.08$), with significant increased concentrations of high-density lipoprotein (1.7 ± 0.3 nmol/l vs 1.2 ± 0.4 nmol/l, $p < 0.01$).

Table 1
Clinical details of the patients

Variable	Atorvastatin	Placebo
Age (year)	54 ± 4.4	55 ± 5.1
Male sex, *n* (%)	15 (75)	17 (85)
Current smokers, *n* (%)	6 (30)	7 (35)
Hypertension, *n* (%)	9 (45)	11 (55)
NYHA class, *n* (%)		
I	2 (10)	1 (5)
II	12 (60)	13 (65)
III	6 (30)	5 (30)
Preoperative drugs		
Beta-blockers	6	5
Ca^{2+} channel blockers	9	11
Nitrates	14	16
Total CPB time (min)	93 (5.8)	100 (10.2)
Aortic cross clamp (min)	45 ± 4.6	49 ± 7.2
Number of grafts	2.3 ± 0.4	2.3 ± 0.6
Total cholesterol (mmol/l)		
Pre-treatment	6.2 ± 1	6.0 ± 0.9
Post-treatment	5.4 ± 0.6	5.9 ± 1.1
HDL cholesterol (mmol/l)		
Pre-treatment	1.2 ± 0.4	1.2 ± 0.7
Post-treatment	1.7 ± 0.3	1.2 ± 0.9
Triglycerides (mmol/l)	2.2 ± 0.3	1.6 ± 0.2

Values are *N* or mean (SD). CPB, cardiopulmonary bypass; HDL, high-density lipoprotein; NYHA, New York Heart Association.

5.1. Hemodynamic and pulmonary function measurement

There were no operative deaths, and no patient sustained a Q-wave myocardial infarction or sub-endocardial myocardial infarction. Mean arterial pressure, heart rate, central venous pressure, pulmonary artery pressure, and cardiac index (CI) were recorded routinely during the experiment. Repeated measures ANOVA revealed that differences were not significant over time within groups and between groups for heart rate, mean arterial pressure, central venous pressure, and CI (Table 2). The mean infusion rate of either vasodilators or dopamine during the same period was the same. There were no differences between the groups with regard to the total volume administered, the mean urinary output, the need for diuretics, and the total fluid balance during the postoperative period. Total blood loss and transfusion requirements in terms of packed cells, fresh-frozen plasma, and platelets were comparable between the

Table 2
Postoperative hemodynamic

	Group	4 h po	12 h po	24 h po	36 h po
HR (beats/min)	Control	88.7 ± 10.1	85.7 ± 10.8	86 ± 9.6	89 ± 11.3
	Statin	86.2 ± 8.9	83.3 ± 10.0	88.6 ± 8.8	86.4 ± 10.4
MAP (mmHg)	Control	83.5 ± 12.8	79.1 ± 10.8	84.9 ± 11.5	85.3 ± 11.7
	Statin	79.8 ± 10.3	82.2 ± 11.1	83.3 ± 12.0	86.1 ± 10.5
CVP (mmHg)	Control	6.9 ± 0.6	7.0 ± 0.8	7.1 ± 08	7.1 ± 0.5
	Statin	7.1 ± 0.7	7.2 ± 0.7	7.3 ± 0.6	7.2 ± 0.9
CI (l min^{-1} m^{-2}))	Control	2.5 ± 0.5	2.6 ± 0.5	2.6 ± 0.8	2.7 ± 0.6
	Statin	2.4 ± 0.4	2.5 ± 0.5	2.7 ± 0.6	2.8 ± 0.8

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index.

two groups. One patient in the placebo group needed a surgical revision for bleeding.

The postoperative course in all groups showed no significant difference in intubation time, infection rate, length of ICU, or hospital stay. Two patients in the placebo group had prolonged ventilation.

6. Results

6.1. Endothelial function

During the course of therapy, no adverse effects were observed in our patients, and clinical laboratory testing revealed no abnormal changes due to atorvastatin therapy. The average basal brachial artery diameter was virtually the same in each group (placebo 3.9 ± 0.2, statin 4.0 ± 0 .3, $p = 0.3$).

At baseline evaluation, a significant difference was found between the coronary patients and those in the normal group; with the exception of six patients in the statin groups, all patients in the coronary groups had an altered endothelial-dependent FMD (normal $10.3 \pm 1.8\%$ vs coronary $4.1 \pm 1.6\%$, $p < 0.01$). Fig. 1 shows the endothelium-dependent dilatation in the two treatment groups. At baseline, the patients of statin group showed a significantly better baseline endothelium-dependent dilatation compared with patients taking placebo (statin $4.7 \pm 1.8\%$ vs placebo $3.4 \pm 1.1\%$, $p = 0.01$). Postoperatively, all patients exhibited a significant reduced endothelial-mediated dilatation at 48 h (statin $2.8 \pm 1\%$, $p < 0.01$ vs baseline; placebo 1.3 ± 0.6, $p < 0.01$ vs baseline), although the FMD was significantly lower in the patients taking placebo compared with those of the statin group ($p = 0.002$). Fig. 2 shows the percent decrease of FMD in the two groups of patients. Compared with baseline values, the endothelium-dependent dilatation showed a drop of $60.1 \pm 15\%$ in patients of the placebo group compared with $45.8 \pm 16.6\%$ in the statin group. At the measurements effected 5 days postoperatively, the values of endothelium-mediated FMD showed a trend toward the respective baseline values in the patients of the two groups. In univariate analysis, FMD was significantly correlated with baseline vessel size, age, and statin therapy group but not with total cholesterol, HDL and LDL cholesterol, smoking, sex, and length of CPG (Table 3). In multivariate analysis, the only significant explanatory variables for FMD were the group variables for statin therapy ($p = 0.012$) and age ($p = 0.015$).

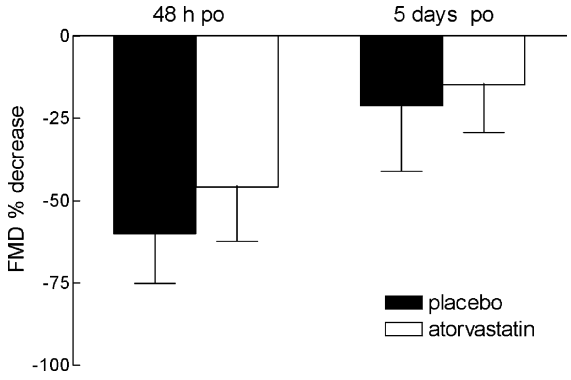

Fig. 2. Percent change over baseline values in flow-mediated, endothelium-dependent vasodilatation of the brachial artery at 48 h, and 5 days post-operatively (po). Each bar represents mean (SD); $p < 0.05$ versus control.

Table 3
Univariate analysis for determinants of FMD and selected explanatory variables

Variables	Coefficient	p
Age	−0.44	<0.01
Sex	0.11	0.31
Smoke	0.17	0.11
Baseline artery size	−0.26	0.02
Total cholesterol	−0.22	0.3
HDL cholesterol	0.89	0.4
LDH cholesterol	−0.13	0.26
Length of CPB	−0.6	0.5
Statin therapy group	0.7	<0.01

Endothelium-independent vasodilatation (nitroglycerin-induced dilation) at baseline was significantly lower in the patients with coronary artery disease than in the normal group ($8.6 \pm 3\%$ vs $15. \pm 2.8\%$, $p < 0.01$), whereas it did not differ significantly between patients taking statins and those in the placebo group (placebo $8.2 \pm 3\%$ vs statin $9.0 \pm 2.9\%$, $p = 0.4$). In contrast to hyperemic FMD, the nitroglycerin-

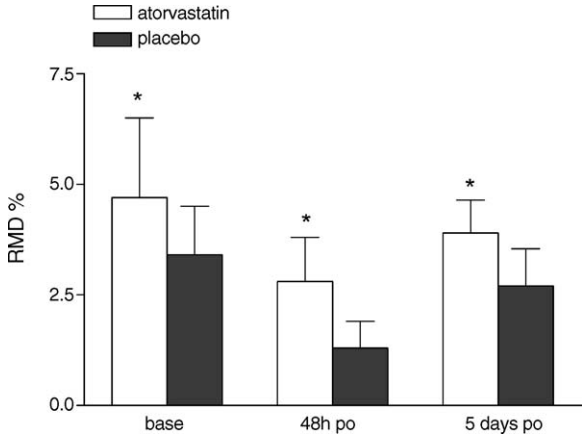

Fig. 1. Flow-mediated dilatation of the brachial artery induced by reactive hyperemia: preoperatively (base), 48 h, and 5 days postoperatively (po). Each bar represents mean (SD); $^{*}p < 0.05$ versus control.

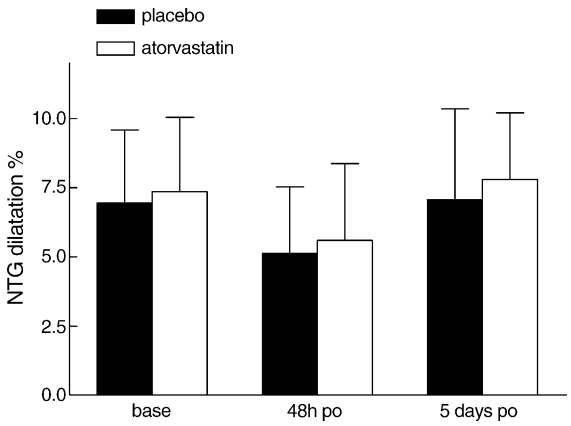

Fig. 3. Nitroglycerin-mediated vasodilatation of the brachial artery: preoperatively (base), 48 h, and 5 days postoperatively (po). Each bar represents mean (SD).

induced dilation was not significantly influenced by extracorporeal circulation as well as by any treatment regimen (Fig. 3). These findings indicate that flow-mediated, endothelium-dependent vasodilatation is significantly impaired in the brachial artery of patients after CPB, whereas endothelium-independent vasodilatation of this vessel is preserved.

7. Discussion

The present study confirms that brachial artery FMD response to reactive hyperemia, a function of endothelial-dependent rather than endothelial-independent vasodilation in systemic resistance vessels, is significantly impaired in patients undergoing coronary surgery with cardiopulmonary bypass [5]. However, it is relatively preserved by pre-treatment with atorvastatin, by a mechanism that is independent of the statin efficacy in lowering serum cholesterol. The reactivity to NTG, although basically reduced compared with normal individuals, was maintained in both the early and postoperative period, indicating that the reaction of the vascular smooth muscle cell to NO is not significantly affected by CPB.

In line with our expectancies, the preoperative endothelium-dependent dilatation was significantly blunted in the coronary patients compared with the normal patients. This observation is confirmative of many past studies showing that coronary artery disease and its correlated risk factors, like advanced age, male sex, dyslipidemia, hypertension, and smoke, are associated with a reduced flow-mediated dilation of the brachial artery [16,17]. In this study it was demonstrated for the first time that the treatment with atorvastatin markedly reduced the drop of endothelium-dependent FMD observed after cardiopulmonary bypass, without significantly affecting the nitroglycerin-induced vasodilatation. The results here confirmed previous observation about the statin efficacy in improving endothelium-dependent FMD of the brachial artery in hypercholesterolemic individuals, independently of its efficacy in lowering the cholesterol levels. Simons et al. [13] demonstrated the efficacy of atorvastatin in improving FMD response in patients with severe primary hypercholesterolemia. In a similar subset of patients, Perticone et al. [14] reported a significant improvement of acetylcholine-mediated vasodilatation after a 4-week treatment with atorvastatin.

In contrast to our expectancies, we found that the endothelium-independent vasodilation was also significantly reduced in coronary patients compared with the patients without cardiovascular risk factors, and the treatment with atorvastatin failed to achieve any improvement. Although the results of previous studies show a preserved smooth muscle function in small series of patients with impaired endothelial function during the first phase of the atherosclerosis [18,19], nevertheless more recent studies on larger patients series report an impaired arterial response to NTG in presence of traditional risk factors for atherosclerosis. Adams et al. [20] reported that a smooth cell dysfunction occurs independently of endothelial-dependent dysfunction in a study on 800 asymptomatic patients with positive risk factors for atherosclerosis. In smaller subset of patients with similar characteristics, Zhang et al. [16] observed an impaired NTG-induced dilation, which was significantly correlated with age, sex, and baseline vessel size. Therefore, it is possible to speculate that structural changes and functional remodeling of the vessel wall could be the cause of the smooth muscle dysfunction in patients with CAD, with the changes becoming evident rather late in the process and being usually preceded by endothelial dysfunction [20,21].

Although the characteristics of the present study do not clarify which pathway is influenced by statins, a number of recent reports suggest a link between these endothelium protective effects of statins and the enhanced expression of endothelial nitric oxide synthase. Laufs et al. [22] have shown that simvastatin and lovastatin improve the stability of the mRNA for eNOS and increase the half-life of the mRNA for eNOS from 13 to 38 h, with a consequent enhanced generation of NO from the endothelium. Wassmann et al. [23] showed that 30 days of treatment with atorvastatin in normocholesterolemic, spontaneously hypertensive rats caused an up-regulation of eNOS mRNA expression (138 $\pm$ 7% of control) and an enhanced eNOS activity in the vessel wall (209 $\pm$ 46% of control). Moreover, treatment with atorvastatin caused a significant reduction in systolic blood pressure and a profound improvement in endothelial dysfunction mediated by a reduction in free radical release in the vasculature. Up-regulation of endothelial NO synthesis, as well as inhibition of hypoxia mediated inhibition of NOS activity, has been observed with simvastatin and lovastatin in mice subjected to cerebral ischemia–reperfusion. These effects were dependent on enhanced NO formation because they failed to ameliorate the high leukocyte rolling and adherence in eNOS deficient mice [24]. Finally, in a past study [25], in an experimental model of hypoxia-reoxygenation we demonstrated that pre-treatment with simvastatin resulted in a significant down-regulation of both P-selectin expression on endothelial cells and CD18 on stimulated neutrophils, by an NO-mediated mechanism. In fact, the addition of L-NAME, an inhibitor of NO synthase, in the culture media of vein segments almost completely abolished the statin effect on neutrophil–endothelial adhesion, indicating an action mediated by enhanced NO synthesis.

8. Limitations of the study

For a clinical point of view, we failed to find significant difference in the postoperative parameters between the two groups of patients, as well as any changes in basal or stimulated flow in coronary grafts. With this regard, it is important to consider that this was a relatively low risk population and none of the 40 patients had any adverse effects during or after their myocardial revascularization procedures. The number of low risk patients enrolled in this study was chosen as to have sufficient power to delineate differences in endothelial functions based on our previous experience with CPB. Therefore, it is probable that the sample size of the present study is not sufficient to assess clinical outcomes such as intubation time, stay in ICU, and postoperative pulmonary morbidity, which are low in our low-risk patients. Atorvastatin may be more beneficial for high-risk patients with complex, prolonged surgical procedures or

with compromised pulmonary function. Finally, we tested the endothelial reactivity in the brachial artery. However, we cannot affirm that changes observed at this levels correspond to the endothelial of the pulmonary or coronary arteries; this latter, in addition to CPB, is subjected to cardioplegia, surgical manipulation, significant ischemia—reperfusion injury, and sometimes preoperative ischemia from CAD.

9. Conclusions

In this study, we have demonstrated that forearm endothelial dysfunction following cardiopulmonary bypass can be significantly improved by atorvastatin treatment. An important aspect of this study is the demonstration that vascular changes occur independently of the statin efficacy of controlling serum cholesterol levels; the possible explanation is that improvement of endothelial function might not be due solely to a decrease in serum cholesterol.

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