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**The effect of LDL apheresis on ocular microcirculation in patients with  
hypercholesterolemia-A pilot study**

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## **Abstract**

### **Aim**

To investigate the effect of LDL (low density lipoprotein) apheresis on ocular microcirculation in patients with hypercholesterolemia

### **Methods**

Six patients with hypercholesterolemia were included in this study. The diameter of retinal vessels was measured continuously with the retinal vessel analyzer (RVA) before and after LDL apheresis. After baseline assessment a monochromatic luminance flicker was applied to evoke retinal vasodilation. Flicker response was then analyzed 50, 70 and 120 sec after baseline measurement. Additionally, cholesterol-, HDL-, LDL- and triglyceride level were obtained to find a possible correlation between retinal vessel diameter changes and lipid metabolism before and after apheresis.

### **Results**

The mean diameter of the arterioles at baseline was  $107.6 \pm 2.1 \mu\text{m}$  and the mean diameter of the venules at baseline was  $132.8 \pm 3.2 \mu\text{m}$ . The diameter of the arterioles after apheresis increased to  $111.2 \pm 2.3 \mu\text{m}$  after 50 sec, to  $113.2 \pm 2.6 \mu\text{m}$  after 70 sec and to  $113.7 \pm 2.6 \mu\text{m}$  after 120 sec showing a trend to statistical significance at all time points ( $P=0.046$ ,  $P=0.028$  and  $P=0.028$ ). The mean diameter of the venules after apheresis increased to  $138.8 \pm 5.9 \mu\text{m}$  after 50 sec, to  $139.8 \pm 6.3 \mu\text{m}$  after 70 sec and to  $141.2 \pm 6.0 \mu\text{m}$  after 120 sec showing a trend to statistical significance at all time points (all  $P = 0.028$ ).

**Conclusions**

Changes in retinal vascular calibre seem to be associated with the systemic effect of a single LDL apheresis. Vasodilatation of the arterioles and the venules improved after LDL apheresis indicating an improvement of ocular perfusion in patients with hypercholesterolemia.

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**Competing Interest:** None to declare

**Key words:** LDL-apheresis, retinal vessel analyzer (RVA), microcirculation

## **Introduction**

LDL (low density lipoprotein) apheresis has become a valid treatment modality for patients with severe hypercholesterolemia in whom a maximal dietetic and drug treatment did not lead to a sufficient decrease of LDL-cholesterol (LDL-C) (1). Most patients undergoing this therapy suffer from a manifest coronary heart disease, another atherosclerotic vascular disease (e.g. peripheral arterial disease) or an enhanced risk for retinal vessel occlusions with a consecutive impairment of micro- and macro-perfusion of end organs. A consequence of the hypercholesterolemia-induced microvascular responses is an enhanced vulnerability of the microcirculation to the effects of ischemia and other inflammatory conditions (2).

Besides LDL lowering effect, a single LDL-apheresis treatment was already reported to positively influence and improve myocardial (3-5) and cerebral blood flow (6).

Other studies demonstrated a substantial reduction of hemorheologically relevant peptides and as a consequence thereof, a reduction of whole blood viscosity and erythrocyte aggregation rate (7-8) contributing to an increase of blood flow by an enhanced release of nitric oxide (NO) from the endothelium (9).

Against this background it seems conceivable that not only the myocardial and the cerebral perfusion is affected by LDL apheresis but also the retinal microcirculation as the retinal vessels mirror the morphology and function of systemic diseases.

Therefore, the aim of the present study was to investigate whether LDL apheresis shows an impact on retinal autoregulation in patients with hypercholesterolemia using the retinal vessel analyzer (RVA).

## **Methods**

Six patients with hypercholesterolemia were included in this study. The study protocol was approved by the ethics committee of Dresden following the declaration of Helsinki. All subjects signed an informed consent before participating in this study. All patients were recruited from the Dresden Apheresis center of the department of internal medicine of the University Hospital Carl Gustav Carus, Dresden and were undergoing LDL apheresis regularly at this center.

### **I. LDL apheresis**

LDL apheresis was performed at the LDL-Apheresis center Dresden using one of four available methods which are described elsewhere in detail and which differ with respect to acute relative reductions in LDL cholesterol (1). Briefly, one patient received DALI (Directly absorbs atherogenic lipoproteins, Fresenius Medical Care, St. Wendel, Germany, ADS 4008) treatment, 1 patient received LF (Lipidfiltration, Octo Nova, Cologne, Germany) treatment and four patients received immunoabsorption (IA, Miltenyi, Bergisch-Gladbach, Germany, Life 18). Plasma and serum samples were obtained before and immediately after LDL apheresis for analysis of lipoproteins and triglycerides (HDL, LDL). Clinical chemistry was measured using standard procedures.

### **II. Retinal Vessel Analyzer**

Initially (approximately at 8.00 a.m., before LDL apheresis) patients were referred to the department of ophthalmology for retinal vessel imaging using the retinal vessel analyzer (RVA). Patients had to pass an ophthalmic examination including slit-lamp biomicroscopy, indirect funduscopy and measurement of intraocular pressure (IOP)

with Goldmann applanation tonometry. Patients with glaucoma, age-related macula degeneration, other ocular diseases and previous intraocular surgery were not allowed to participate in this study. After the first retinal imaging, LDL apheresis was performed in the LDL-Apheresis center and at approximately 2.00 p.m. second retinal imaging (after LDL apheresis) was performed. All measurements were undertaken in the right eye after using tropicamid 0.5% (Mydrum, Ankerpharm) for pupil dilatation according to the following time schedule: After a short resting period to obtain stable hemodynamic conditions, diameter measurements with the RVA were performed. Retinal vessel diameters were continuously measured for 352 seconds. Diffuse luminance flickering light was applied consecutively at 50, 70 and 120 seconds. Before and after each flicker period 60 seconds of baseline recordings were scheduled.

Retinal vessel imaging was evaluated with the retinal vessel analyzer (RVA). The RVA is a commercially available system that comprises a fundus camera (Zeiss FF 450, Jena, Germany), a video camera, a high resolution recorder, a real time monitor, and a personal computer with a vessel diameter analyzing software. The RVA allows the precise determination of retinal vessel's diameter with a time resolution of 25 readings/sec. Retinal irradiance was approximately  $220 \mu\text{m} \times \text{cm}^{-2}$ , which is approximately 50 times lower than the maximum level allowed for constant illumination of the retina at the wavelengths mentioned below. The system provides excellent reproducibility and sensitivity (10). In the present study, a major temporal artery and vein was studied. Measurement of retinal vessel diameters was taken between 1 and 2 disc diameters from the margin of the optic disc.

### **III. Flickering light stimulation**

For flicker stimulation a custom built device was used, stimulating with light flashes at a frequency of 8 Hz. Flicker was generated by focusing the light of a 150 W halogen light source on a rotating sector disc producing a square wave light pattern with a modulation depth of 100 %. Using an optical fibre, flicker stimuli were delivered to the eye through the illumination pathways of the fundus camera by the RVA. The flicker was centered in the macula with an angle of approximately 30 degrees.

A wavelength -separation technique was used to spectrally separate the flicker light from that used to illuminate the fundus. For flicker stimulation, white light in combination with a 550 nm low pass cut-off filter was used. This ensures that only light with wavelengths below 550 nm is used for flicker stimulation. To separate the flickering light from the light illuminating the fundus, an interference filter with a center wavelength of 577 nm and a bandwidth of 10 nm (Laser components, Olchingen, Germany) was placed in front of the light source of the fundus camera. This window was chosen because in this spectral range the contrast between blood vessels and the surrounding tissue is optimal. A retinal irradiance of approximately  $220 \mu \text{Wcm}^{-2}$  was used to achieve optimal fundus images. A second interference filter which exactly matches the one in the illumination pathway is placed in front of the video camera. This ensures that the light used for flicker stimulation does not reach the CCD chip of the video camera but is perceived by the subject under study (11-14).

### Statistical analysis

Statistical analysis was performed using the software SPSS (version 15.0).

Changes in retinal vessel diameters were expressed as the absolute diameter changes and percent changes over baseline values. Baseline values were calculated as an average of the last 30 seconds before start of the flicker stimulation. Flicker



response of the 50 seconds flicker period was calculated as an average of the last 10 seconds of stimulation period, for the 70 seconds of the stimulation period as an average of the last 20 seconds of the stimulation period and for the 120 seconds stimulation as an average of the last 30 seconds of the visual stimulation. Due to the small number of patients the non-parametric Wilcoxon test for paired samples was performed. A  $P < 0.05$  was considered as the level of significance. Due to multiple testing the P-value was adjusted according Bonferroni to  $P=0.05/3$ . Data are presented as the mean  $\pm$  SD.

## Results

Six patients were included in this study (4 women, 2 men). Mean age of all patients was 60.3 years (range: 46-71 years).

The mean diameter of the arterioles before apheresis was  $107.5 \pm 2.1 \mu\text{m}$  at baseline,  $107.7 \pm 1.9 \mu\text{m}$  after 50 sec,  $109.6 \pm 2.1 \mu\text{m}$  after 70 sec and  $107.5 \pm 1.9 \mu\text{m}$  after 120 sec. The mean diameter of the arterioles increased after apheresis to  $111.2 \pm 2.3 \mu\text{m}$  after 50 sec ( $P= 0.046$ ), to  $113.2 \pm 2.6 \mu\text{m}$  after 70 sec ( $P=0.028$ ) and to  $113.7 \pm 2.6 \mu\text{m}$  after 120 sec ( $P= 0.028$ ) showing a trend to statistical significance at all time points (Fig.1).

The mean diameter of the venules before apheresis was  $132.8 \pm 3.2 \mu\text{m}$  at baseline,  $133.8 \pm 3.0 \mu\text{m}$  after 50 sec,  $134.0 \pm 2.6 \mu\text{m}$  after 70 sec and  $134.2 \pm 2.6 \mu\text{m}$  after 120 sec. The mean diameter of the venules significantly increased after apheresis to  $138.8 \pm 5.9 \mu\text{m}$  after 50 sec ( $P= 0.028$ ), to  $139.8 \pm 6.3 \mu\text{m}$  after 70 sec ( $P=0.028$ ) and to  $141.2 \pm 6.0 \mu\text{m}$  after 120 sec ( $P= 0.028$ ) showing a trend to statistical significance at all time points (Fig.2).

Figure 3 shows the overall flicker-induced vasodilatation changes in % of the arterioles and the venules before and after apheresis revealing statistical significance for the arterioles ( $P=0.028$ ) and the venules ( $P=0.028$ ).

Table 1 indicates the lipid and blood pressure changes before and after apheresis which revealed that cholesterol-, HDL-, LDL- and the triglyceride level significantly decreased ( $P=0.028$ ) after apheresis treatment. Systemic blood pressure (systolic and diastolic) did not any reveal any significant changes  $P=0.197$  ( $P=0.414$ ) before and after apheresis. Pulse per minute significantly increased after apheresis ( $P=0.038$ ).

Correlation analysis of lipid parameters and blood pressure changes and diameter changes of the retinal vessels did not reveal any significant associations ( $P$ -values not shown).

## **Discussion**

The results of the present study clearly demonstrated an improvement of flicker-induced vasodilatation after a single LDL apheresis treatment in the retinal arterioles and in the venules which was statistically significant in the overall vasodilatation response. Our observation showed that a single LDL apheresis led to an increase of retinal blood flow which was well detectable by the flicker response of the retinal vessel analyzer (RVA). To date, previous studies investigating the microcirculation in other organs showed an improvement in coronary flow reserve and thus myocardial perfusion in patients with coronary heart disease, hypercholesterolemia and in heart transplant recipients (15-17) after single apheresis treatment, presumably by improving the NO- and acetylcholine (ACH)-mediated endothelial vasodilatation (5).

In retinal vessels the vasodilatory response to diffuse luminance flicker stimulation seems to be mediated by endothelial nitric oxide (10), too, indicating that the local production of nitric oxide in the retinal vessels increases after apheresis, leading to an improvement of vasodilatation and retinal endothelial function in these patients. Our finding is supported by observations of Tamai and colleagues who described an increase of endothelium-dependent vasodilatory response in forearm blood flow associated with increased local production of nitric oxide metabolites (19).

According to the law of Hagen-Poiseuille, the microcirculation is directly proportional to the product of vascular radius to the power of four and blood pressure divided by the product of viscosity and vessel length (20). As vessel length is rather constant, the three other parameters could theoretically be influenced by LDL apheresis.

Different studies reported a substantial reduction of hemorheologically relevant peptides like fibrinogen by up to 60 % by reducing plasma viscosity (by < 20 %) and erythrocyte/ thrombocyte aggregation (by > 60 %) and leading to a significant improvement of micro-perfusion in the brain and the skeletal muscle (21-22). The vessel radius is affected by several different factors, some of which are influenced by LDL apheresis. Kojima et al. demonstrated in two patients treated with dextran sulphate adsorption (DSA) an increase of NO-levels using heparin as an anticoagulant (9).

Another major mechanism being proposed to be involved in endothelial dysfunction in patients with hypercholesterolemia is the presence of a large number of circulating inflammatory oxidative stress markers such as inflammatory cytokines, cellular adhesion molecules, acute phase reactants and C-reactive protein (CRP) which are significantly reduced by LDL-apheresis (23-24). Interestingly, in a recent study by Ramunni et al. in 23 patients with nonarteriitic ischemic optic neuropathy three weekly sessions of LDL apheresis resulted in a reduction of circulating markers of

endothelial dysfunction, and this reduction was correlated to a significant improvement in visual fields (25).

In our study both, arterioles and venules reacted with a vasodilatation to flicker light which was, however, slightly stronger in the venules than in the arterioles. Here, it needs to be noted that the prevalence of hypertension was high among our patients but all patients showed only mild hypertensive fundoscopic retinal changes similar to a fundus hypertonicus grade 1, indicating a well controlled blood pressure. It remains unclear whether these changes of retinal arterial vessels would also have been observed in patients with an uncontrolled hypertensive blood pressure with more prolonged fundoscopic hypertensive changes. Moreover, looking at the baseline values of the arteries and venules before and after apheresis showing nearly equal diameters indicates that the effect of LDL apheresis might only be of short duration but can be provoked by flicker light only. To the best of our knowledge, there are no sufficient data dealing with the duration of apheresis therapy on blood perfusion, neither in the cerebrum nor in the skeletal muscle or in the eye. Unfortunately, we also did not perform retinal vessel analysis on these patients after a longer follow-up period after initial apheresis treatment to detect possible long lasting vascular changes.

One major limitation of this study is certainly the number of patients being included in this pilot study. The changes of retinal vessels` diameter after LDL apheresis showed a trend towards statistical significance. Except from the overall vasodilatation response (Fig.3), a statistical significance could, however, not be obtained, which might be related to the small number of patients in this pilot study. By increasing the sample size in future studies it is conceivable that the level of the P-value might even more improve and we would obtain more significant results. As a consequence, we were also not able to perform multiple testing to reveal possible associations between

LDL parameters and vessel's diameters. Our study was, however, not designed for this outcome analysis, and a larger sample size may be required to investigate these issues.

Secondly, for ethical reasons, we could not justify performing LDL apheresis in healthy control subjects. Therefore, we cannot say whether apheresis also produces hemodynamic effects in the absence of hypercholesterolemia. However, plasma exchange (another procedure that acutely removes LDL), performed for reasons other than hypercholesterolemia, was associated with unmodified cerebral blood flow, as evaluated by the radioactive xenon technique (26).

Thirdly, employing the RVA, only information about vessel diameter and the reactivity of retinal vessels to flicker stimulation was available. However, given that our measures were done in one single artery and vein and not in all visible vessels, our data do not represent total cross-sectional retinal vessel diameters. In extrapolation, for determination of changes in blood flow per se, information about blood velocity would be required. In principle, this information could be gained using laser doppler flowmetry (LDF).

The fourth limitation of our study is that all our patients received LDL apheresis for several years so that our study results may not represent the effects of an early single apheresis nor depict longitudinal changes. However, a previous study by Mellwig and co-workers comparing initial and chronic LDL apheresis therapy in patients with coronary artery disease revealed similar improvements of coronary perfusion after a single apheresis in the two treatment groups (5).

Taking together, for the first time in this pilot study an improvement of flicker-induced vasodilatation of retinal arterioles and venules was detected in patients with hypercholesterolemia after a single LDL apheresis. Our results indicate that ocular

blood perfusion is substantially affected by the systemic effect of LDL apheresis in patients suffering from hypercholesterolemia.

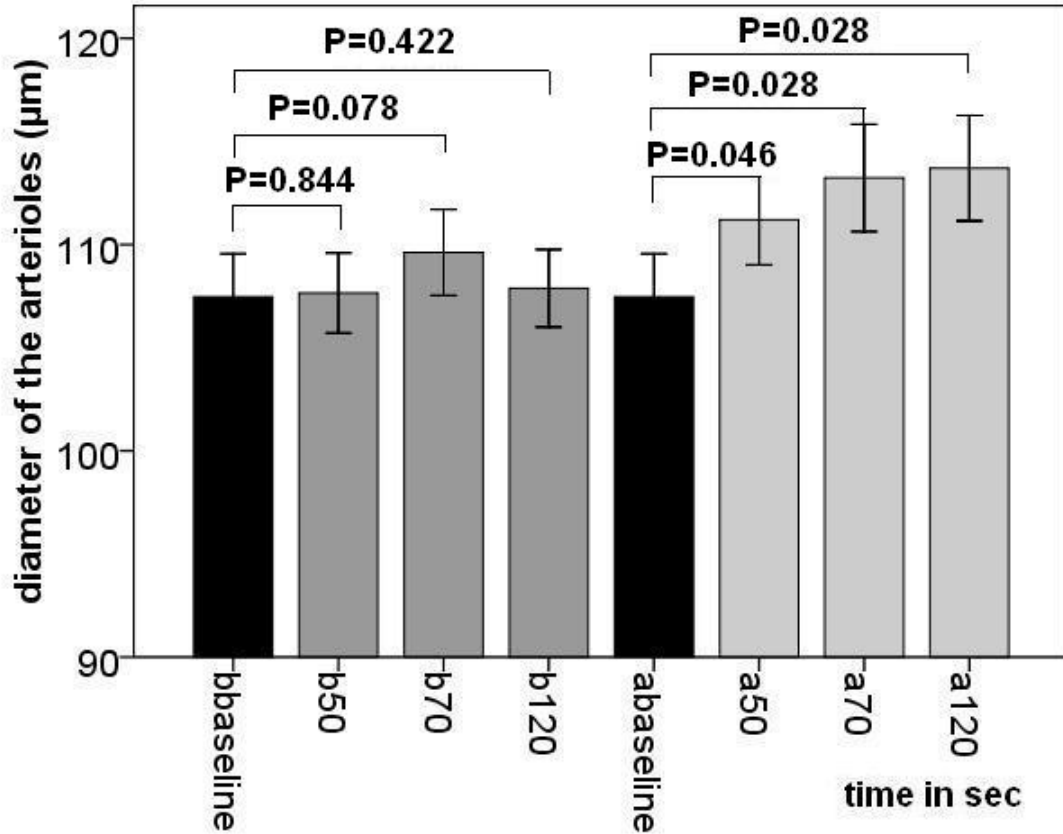
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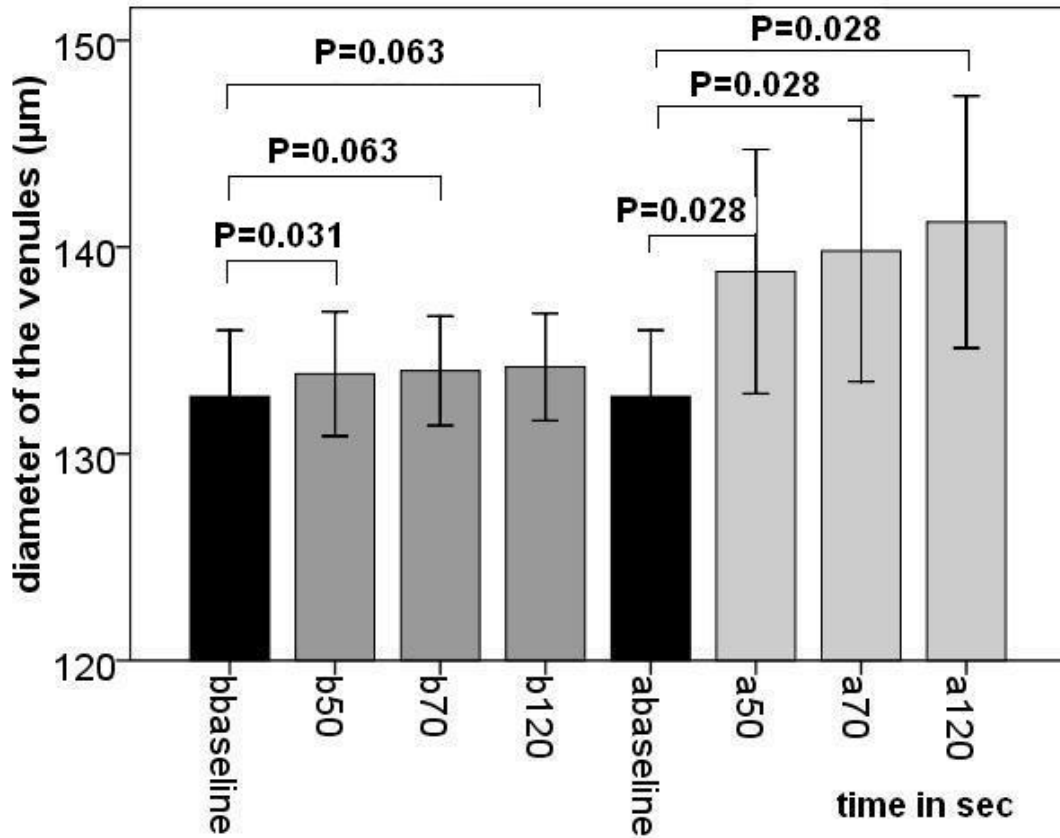
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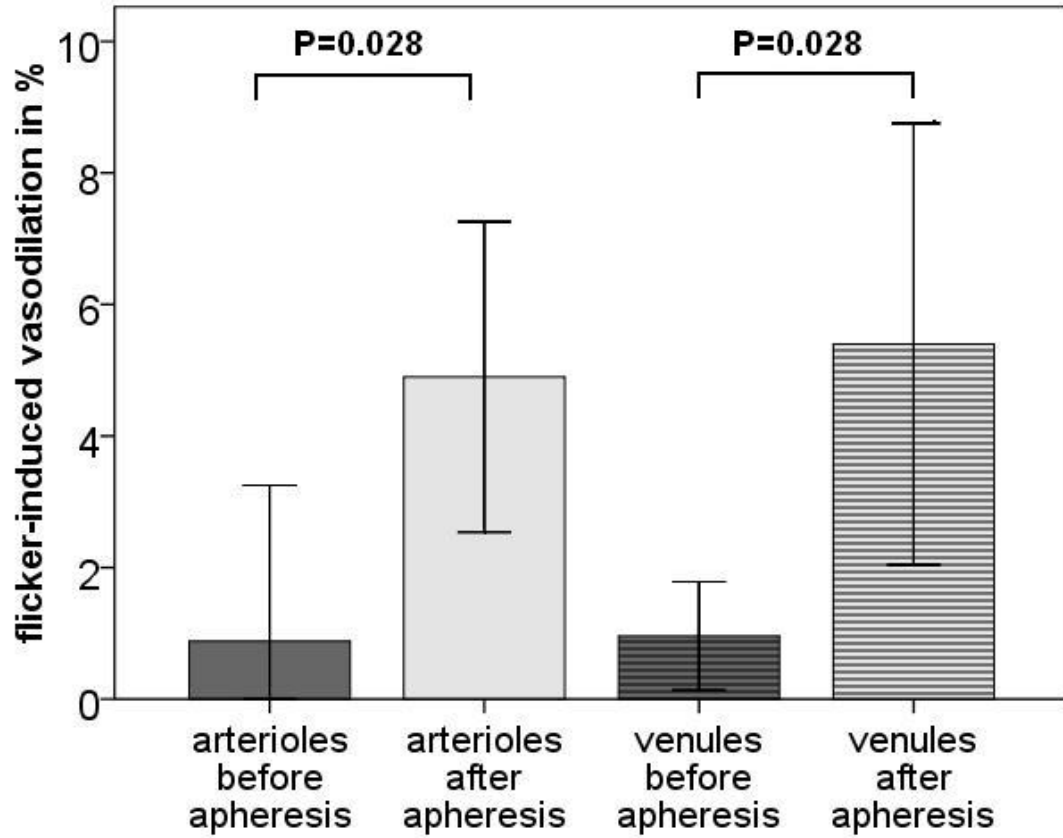
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**Figure 1** Diameter changes of the arterioles ( $\mu\text{m}$ ) before LDL apheresis at baseline (bbaseline), after 50 sec (b50), after 70 sec (b70), after 120 sec and after LDL apheresis at baseline (abaseline), after 50 sec (a50), after 70 sec (a70) and after 120 sec (a120)



**Figure 2** Diameter changes of the venules ( $\mu\text{m}$ ) before LDL apheresis at baseline (bbaseline), after 50 sec (b50), after 70 sec (b70), after 120 sec and after LDL apheresis at baseline (abaseline), after 50 sec (a50), after 70 sec (a70) and after 120 sec (a120)



**Figure 3** Flicker-induced vasodilatation changes in (%) in arterioles and venules before and after LDL apheresis

<b>Parameter</b>	<b>Before apheresis</b>	<b>After apheresis</b>	<b>P-Value</b>
<b>Cholesterol (mmol/l)</b>	4.1 ±1.6	2.1 ± 0.7	0.028
<b>HDL (mmol/l)</b>	1.5± 0.6	1.1±0.5	0.028
<b>LDL (mmol/l)</b>	3.2 ± 1.4	0.8 ± 0.3	0.028
<b>Triglycerides (mmol/l)</b>	1.8 ± 0.9	0.9 ± 0.6	0.028
<b>RRsyst (mmHg)</b>	135 ± 17.3	125.8 ± 27.1	0.197
<b>RRdiast (mmHg)</b>	79.2 ± 8.0	76.6 ±8.2	0.414
<b>Pulse (min<sup>-1</sup>)</b>	65.3 ± 6.0	70.0 ± 7.4	0.038

**Table 1** Lipid and blood pressure parameters before and after LDL apheresis, (SD)