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Short-term high-intensity interval training improves micro- but not macrovascular function in hypertensive patients

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Introduction: Arterial hypertension is a global health burden that affects vascular structure and function. Assessment of endothelial function can improve cardiovascular (CV) risk stratification. Exercise treatment reduces over all CV risk and improves vascular health. However, it is still not clear which part of the vascular bed is most sensitive to exercise treatment in patients with CV risk. This study aimed to investigate the effects of an 8-week walking based and supervised high-intensity interval training (HIIT) on macro- and microvascular endothelial function as add-on therapy in patients with arterial hypertension.

Methods: Forty patients (mean age 58 ± 7 years) treated for arterial hypertension were randomized in the HIIT (3×/week) or control group (CG) receiving standard physical activity recommendations. Arteriolar (aFID) and venular (vFID) flicker light-induced dilatation for retinal microvascular and flow-mediated dilatation (FMD) for macrovascular endothelial function were assessed. In addition, standardized assessments of patients' characteristics were performed before and after 8 weeks.

Results: Both groups reduced weight and body mass index but only the HIIT group reduced body fat, visceral fat, and increased peak oxygen uptake after 8 weeks. The control group reduced diastolic blood pressure. No blood pressure changes were found in the HIIT group. Arteriolar FID increased in the HIIT group independently of confounders (pre: 2.40 ± 0.98%, post: 3.19 ± 1.31%, $p < 0.001$) but not in the control group (pre: 3.06 ± 1.50%, post: 2.90 ± 1.46%, $p = 0.280$). No changes were found for FMD in either group.

Conclusion: Arteriolar FID was found to be a sensitive vascular biomarker to assess exercise-induced microvascular improvements even in a short time setting of an 8-week exercise therapy with HIIT. Short-term exercise training affects microvascular endothelial function but not large artery endothelial function. Thus,

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retinal aFID appears to be a sensitive biomarker to detect short-term exercise efficacy on a vascular level. Dynamic retinal vessel analysis as a diagnostic approach may prove to be an ideal candidate vascular biomarker to monitor treatment effects of exercise in patients with hypertension on top of standard clinical care and may support clinical decision-making in the future.

KEYWORDS

exercise, exercise medicine, hypertension, retinal endothelial function, vascular health

1 | INTRODUCTION

Arterial hypertension is an increasing healthcare burden. It is the leading preventable risk factor for cardiovascular (CV) death and all-cause mortality.[1–3] Due to an aging population and a higher exposure to lifestyle risks such as unhealthy diet, lack of physical activity or obesity, the prevalence of hypertension is rising.[4] In 2015, about 8.5 million deaths were associated with arterial hypertension.[5] Forty percent of all annual deaths in Europe are directly associated with arterial hypertension-induced CV diseases.[6] By 2025, the prevalence of patients with hypertension is expected to increase up to 60% of all adults.[7] Hypertension induces structural and functional changes in the macro- and microcirculation, which eventually lead to stiffer arteries.[8] In a simplified model, the inability of adequate adaption of the vessel to higher blood flow or blood pressure is commonly called endothelial dysfunction.[8] Impaired endothelial function is often seen in advanced age groups as age is an effectual CV risk factor. There is clear evidence for a greater and faster vascular aging process in patients with chronic kidney disease,[9] diabetes,[10] and hypertension regardless of age.[11] The asymptomatic and early onset of the disease pose a challenge in the optimal treatment of arterial hypertension.[9] An early detection of changes in endothelial function would allow for an improved estimation of individualized CV risk and a timely initiation of primary and secondary CV prevention.[8] Several non-invasive measurements for macro- and microvascular structure and function are available. Flow-mediated dilation (FMD) is referred to as the gold standard for measuring macrovascular endothelial function.[10] Per percent point increase in brachial FMD a 8–13% lower risk of CV events was found in both high- and low-risk populations[11] although the risk reduction was greater for patients with CV diseases.[12] FMD has been shown to predict CV events,[12] all-cause mortality,[11] and progression in target organ damage in hypertensive patients.[13]

To investigate endothelial function on a microvascular level, dynamic retinal vessel analysis (DVA) can be performed. DVA has previously been shown as a valid and non-invasive technique to quantify systemic CV risk and vascular health.[14–16] DVA quantifies retinal endothelial dysfunction by measuring the flicker light-induced dilatation (FID) of arteriolar and venular vessel segments separately over time. FID is an independent predictor for CV events in patients with CV risk factors[15] and correlates negatively with hypertension-induced endothelial dysfunction and hypertension severity[17] as well as with CV risk factors and diseases such as obesity,[18,19] hypercholesterolemia,[20] age,[21] diabetes,[22] and chronic heart failure.[23] Furthermore, patients with end stage renal disease and lower venular FID had significantly shorter 3 year survival rates (66.9%) compared to patients with higher venular FID (92.4%).[14] We recently published the first normative data and standard operating procedures for DVA assessments to improve CV risk stratification and standardize assessments.[24]

Regular physical activity (PA) has been shown to prevent or delay the onset of hypertension and reduce blood pressure.[25] Furthermore, PA has been shown to reduce CV mortality independently of blood pressure levels[26] and to decrease the risk of developing de novo hypertension.[27] A low cardio respiratory fitness (CRF) is strongly correlated with all-cause mortality and CV risk[28] while improvements in CRF seem to reduce the risk of CV events even in high-risk populations such as patients with coronary disease[29] or heart failure.[30] Aerobic endurance exercise has been defined as the first exercise priority to lower blood pressure in patients with arterial hypertension, indicating that further data are warranted on the blood pressure lowering effects of high-intensity interval training (HIIT).[31] Strong evidence exists that endothelial dysfunction and the pathogenesis as well as the disease severity of hypertension are associated.[32–34] Several vascular biomarkers exist that quantify endothelial dysfunction as described above. To date it remains unclear which vascular biomarker best quantifies exercise treatment effects on endothelial function as essential underlying mechanism to reduce blood pressure as long-term approach. Therefore, the aim of this study was to investigate the short-term effects of an 8-week HIIT, as add-on therapy in patients with hypertension, on blood pressure as well as macro- and microvascular

endothelial function compared to a control group (CG) receiving standard PA recommendations. In addition, we aimed to investigate the effects of HIIT and the control condition on CRF and further patients' characteristics.

2 | METHODS AND ANALYSIS

We recently published the study protocol of the "Hypertension and retinal microvascular dysfunction" (HyperVasc) study with an extensive description of all study procedures.[35] The present study is part of the Hypervasc trial and included 41 patients with hypertension.

2.1 | Study design

Participants were randomized into a HIIT group ($n = 21$) or a control group with PA recommendations ($n = 20$). Equal group sizes in the HIIT and the control group were achieved by blockwise randomization. Randomization was performed after baseline assessments by an independent and blinded research assistant. Enrolment decisions were communicated to the participants by LS.

The study took place at the Department of Sport, Exercise and Health in Basel Switzerland. This study was conducted according to the Helsinki Declaration,[36] approved by the Ethics Committee of Northwest and Central Switzerland (EKNZ-2021-00086) and registered on ClinicalTrials.gov in February 2021 (NCT04763005). All patients singed a written informed consent prior the first assessment. Data collection started end of March 2021 and last patient out was Spring 2022.

2.2 | Inclusion and exclusion criteria

Study participants were recruited via advertisements in local newspapers. Diagnosed hypertensive men and women between 40 and 70 years of age, receiving drug treatment with controlled BP, defined as values ≤159/99 mmHg, were invited to participate. Any CV, pulmonary or inflammatory disease, diabetes, chronic kidney diseases, CV medication (except of antihypertensive medication), changes in antihypertensive medication during the intervention period, smoking, a body mass index (BMI) ≥30 kg/m^2, exercise-limiting musculoskeletal problems and known ophthalmic diseases such as macular degeneration, glaucoma, or high intraocular pressure (IOP) (≥20 mmHg) were exclusion criteria. BP was measured on 2 different days according to the 2018 ESC/ESH hypertension guidelines for blood pressure categorization.[25]

2.3 | Macro- and microvascular assessments

The participants attended the vascular assessment in a fasted state in the morning. They were asked to avoid alcohol and exercising 24 h prior to the measurements and caffeine on the assessment day. Patients were asked to take their daily routine medication. In the vascular assessment at baseline and for image analysis at the end of the study period, the investigators were blinded for group allocation and patients' characteristics. All vascular assessments were performed by one experienced investigator. Extensive description of vascular assessments can be found in the study protocol.[35]

Briefly, FMD was assessed, measuring the brachial artery using a semiautomatic, ECG-guided high-resolution B-mode ultrasound system (UNEX EF 38G, UNEX Corp.) and a BP cuff, which was applied to the forearm of the patient. After a short period of rest, the blood pressure cuff was inflated and cuff pressure increased 50 mmHg above resting systolic blood pressure for 5 min. Before inflation and continuously during the last minute of the inflation period rest diameter of the right brachial artery was measured. Additionally, shear stress induced vascular response was analyzed after cuff-deflation (PC Analysis, UNEX Corp.).

Retinal endothelial function was examined by measuring the arteriolar and venular diameters over time using the Dynamic Vessel Analyzer (DVA®; IMEDOS Systems GmbH) and a fundus camera (450 FF; Carl Zeiss). The gold standard procedure for DVA, as used in this study, was previously defined and described in detail.[24] In brief, arteriolar and venular vessels of the right eye were assessed. Baseline measurements were done to determine mean baseline diameters and to observe inter- and intra-individual variations in vessel diameters.[37] Flicker light was used to provoke the physiological response of increased retinal blood flow and dilation of vessel diameters.[38] Changes in diameter due to the applicated stimulus were calculated automatically by the integrated RVA software (RVA 4.61, IMEDOS Systems GmbH, Jena, Germany) in percent relative to the individual baseline value.[39] Arteriolar (aFID) and venular (vFID) flicker light-induced dilation as well as arteriolar constriction after flicker light (aCON) were investigated to quantify microvascular endothelial function.

2.4 | Anthropometry and cardiorespiratory fitness

Anthropometric data were collected in the morning under fasted conditions. Standard procedures were used

to measure height. Body mass, BMI, and body fat were measured by using the Inbody 720R (JP Global Markets GmbH).[40] Twenty-four hour blood pressure monitoring was performed using the Mobil-O-Graph® device (I.E.M GmbH). IOP was measured using the ICare PRO (Tiolat Oy) rebound tonometer. Venous blood samples were taken and stored at −80°C until further analyses after the data acquisition was completed. Physical fitness was analyzed by an individualized bicycle ramp protocol as described previously.[35,41] Peak oxygen uptake ($\dot{V}O_2$peak) and maximal heart rate (HRmax) were analyzed using the Cortex Metalyzer R 3B metabolic test system (Cortex Biophysik GmbH). Exhaustion was achieved when the predefined respiratory exchange ratio (RER) for the respective age group was reached (40–59 years RER ≥ 1.10; 60–69 years RER ≥ 1.06).[42] If individual exhaustion was not achieved, the ramp protocol was repeated on a separate day.

2.5 | Exercise intervention and control condition

The exercise intervention consisted of an 8-week HIIT with 3 sessions of 45 min per week. The sessions included a 10-min warm-up (60–70% HRmax), a high-intensity interval of 4 × 4 min (80–95% HRmax) with 3 min active recovery (60–70% HRmax) in between followed by a 10-min cool-down (60–70% HRmax). To familiarize the participants to the intensity, the intervention started with a habituation week at 75% HRmax. To monitor heart rate during training, Polar®H7 heart rate sensors and Polar®M400 watches were used. The sessions were supervised by sport scientists, who motivated the participants and controlled the heart rates during and after every training session. The control group received PA recommendations according to the current guidelines of the European Society of Cardiology.[43] Participants of the control group were advised to document their PA behavior in a PA diary. After 4 weeks, their well-being was evaluated by a phone call. According to the current PA guidelines, recommendations were considered fulfilled if at least 450 metabolic equivalents per week were achieved by the participants.[43]

2.6 | Statistical analysis and sample size calculations

The primary outcome of this study was the exercise-induced effect on retinal arteriolar endothelial function measured as aFID. Secondary outcome was macrovascular endothelial function (FMD) and further microvascular parameters of endothelial function (vFID and aCON). Further outcomes were 24 h blood pressure, CRF and further patients' characteristics. Follow-up and baseline patients' characteristics were described through mean and standard deviation. To analyze differences in the HIIT group and the control group, paired sample *t*-tests and analysis of covariance (ANCOVA) were calculated. In addition, we calculated linear regression models adjusted for the corresponding values at baseline, antihypertensive medication at baseline, age, sex, change in blood pressure, change in $\dot{V}O_2$peak, and change in BMI to analyze potential intervention effects. One linear regression model with change of aFID as dependent and change in $\dot{V}O2$peak as independent variable was calculated. For the generation of graphs and for statistical tests with a two-sided confidence interval of 95%, the statistical program R (R Foundation for Statistical Computing, version 3.5.0.) was used.

The sample size calculation is described in detail in our published study protocol.[35] Briefly, we needed 32 participants to reach our target power of 95% with a two-sided significance level of 0.05 for our primary outcome of the Hypervasc study. We included 41 participants to account for potential drop-outs.

3 | RESULTS

After screening for exclusion and inclusion criteria, 41 participants were included in this study and randomized into HIIT or CG (Figure 1). Follow-up assessment was performed in 38 patients (HIIT $n = 19$, CG $n = 19$). HIIT participants included in the final analysis attended the previously described training sessions and met the intensity requirements as described in Section 2.5, with an accuracy of at least 80% in 15 of 19 patients. With one exception, the current PA guidelines were followed in the control group. In both groups, a dropout occurred due to the participant experiencing too much effort. An additional dropout occurred in the intervention group due to a previously unknown eye disease, which was unrelated to exercise training (Figure 1).

3.1 | Patients' characteristics

Antihypertensive medications were comparable between both groups. Patients allocated to HIIT took mainly Renin–Angiotensin–Aldosterone System (RAAS) inhibitors ($n = 15$, 79%) or calcium channel blocker ($n = 4$, 21%). Patients allocated to the CG took mainly RAAS inhibitors ($n = 13$, 68%), calcium channel blocker ($n = 3$, 16%), or beta-blocker ($n = 3$, 16%). Detailed patients' characteristics for both groups at baseline and after the intervention period are shown in Table 1. Both groups reduced weight and BMI but only HIIT reduced body fat (%) and visceral

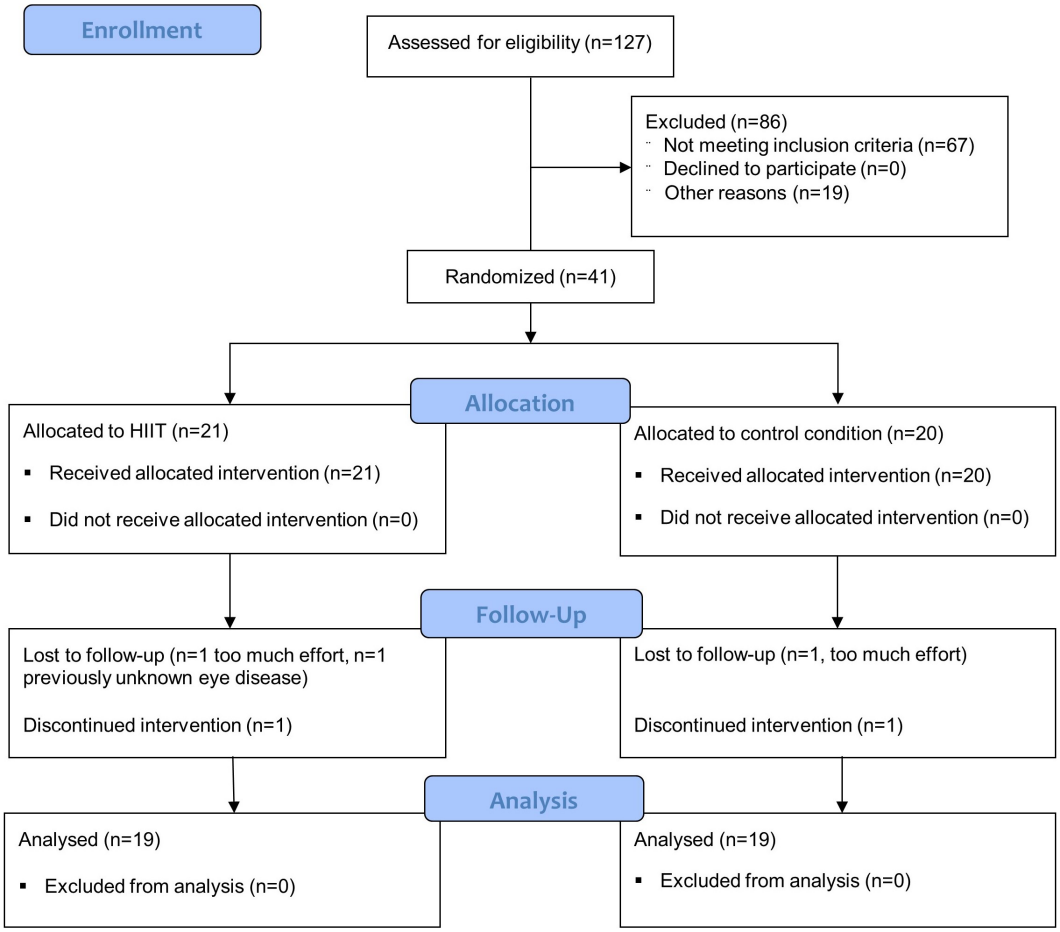

FIGURE 1 Flow chart.

fat. No changes were observed for 24 h blood pressure and muscle mass. CRF measured as $\dot{V}O_2$peak was improved in the HIIT group but not in the CG. Blood glucose in HIIT and low-density lipoprotein in CG were significantly reduced after the intervention period.

3.2 | Vascular biomarkers

The HIIT group showed improved aFID after the intervention compared to the CG and corrected for baseline (Table 2 and Figure 2). The improvement remained statistically significant even after adjustment for age, sex, Δsystolic and Δdiastolic blood pressure, ΔV̇O2peak, and ΔBMI (Table 3). The CG showed no statistically significant changes in aFID. Individual trajectories for FMD and aFID of the HIIT and CG are displayed in Figure S1. There were no statistically significant changes in vFID and aCON for HIIT nor for CG (Tables 2 and 3). Moreover, HIIT and CG showed no statistically significant effects on FMD (Tables 2 and 3). The change in V̇O2peak explained only 3% of aFID adaptations (β [95% CI] 0.06 [−0.02, 0.15] $p = 0.145$).

4 | DISCUSSION

This study, for the first time, showed an improvement of microvascular endothelial function but not large artery endothelial function after short-term HIIT in patients with arterial hypertension independent of changes in CV risk factors.

4.1 | Effects of exercise on endothelial function

DVA has previously been shown to predict CV events.[14–16] Blunted aFID has previously been associated with higher CV risk and long-term mortality rates. The HIIT group in our study showed improved aFID (0.79 percentage points). These improvements are comparable to a previous publication of our group, also showing aFID improvements after 12 weeks HIIT in older patients with multiple CV risk factors aFID.[44] Even if higher aFID values are associated with better CV outcome, long-term follow-up studies are essential to investigate whether exercise-induced aFID improvements are associated with reduced CV risk and

TABLE 1 Sample characteristics in patients with hypertension before and after exercise or control condition.

	Intervention group ($n = 19$) Mean ± SD			Control group ($n = 19$) Mean ± SD			
	Pre	Post	p^a	Pre	Post	p^b	p^c
Age (years)	56 ± 6			59 ± 7			
Sex (f/m)	6/13			8/11			
Weight (kg)	77.5 ± 17.9	76.0 ± 17.3	0.004	77.0 ± 14.0	75.8 ± 14.1	0.017	0.829
BMI (kg/m^2)	25.7 ± 3.1	25.3 ± 3.0	0.003	25.2 ± 2.9	24.8 ± 3.0	0.014	0.940
Body fat (%)	27.0 ± 5.5	25.8 ± 6.1	0.023	28.6 ± 6.8	28.1 ± 7.5	0.266	0.254
Visceral fat area (cm^2)	89.8 ± 26.0	82.6 ± 23.7	0.001	96.7 ± 31.2	93.8 ± 34.1	0.155	0.140
Muscle mass (kg)	31.9 ± 9.1	31.8 ± 9.1	0.616	30.5 ± 6.5	30.2 ± 6.1	0.107	0.203
$\dot{V}O_2$ peak (mL/min/kg)	33.3 ± 5.7	36.7 ± 5.1	<0.001	34.0 ± 9.2	34.2 ± 8.9	0.688	0.002
Max. Watt (W)	211 ± 62	231 ± 64	<0.001	215 ± 74	211 ± 72	0.176	<0.001
Rest. sys. BP (mmHg)	134 ± 9	138 ± 14	0.265	138 ± 19	134 ± 11	0.150	0.095
Rest. dia. BP (mmHg)	87 ± 8	87 ± 9	0.830	88 ± 8	85 ± 7	0.010	0.114
24 h sys BP (mmHg)	129 ± 10	127 ± 10	0.331	128 ± 7	126 ± 9	0.395	0.907
24 h dia BP (mmHg)	85 ± 7	83 ± 6	0.258	82 ± 7	81 ± 7	0.458	0.390
Stress sys. BP (mmHg)	164 ± 20	177 ± 26	0.006	177 ± 16	181 ± 23	0.315	0.164
Stress dia. BP (mmHg)	89 ± 12	86 ± 13	0.290	87 ± 8	85 ± 13	0.237	0.985
Hs-CRP (mg/L)	3.06 ± 6.74	1.36 ± 1.47	0.282	1.43 ± 1.18	1.73 ± 1.54	0.254	0.357
Fasting glucose (mmol/L)	5.29 ± 0.61	4.91 ± 0.51	<0.001	5.31 ± 0.77	5.19 ± 0.82	0.296	0.043
HDL (mmol/L)	1.27 ± 0.38	1.26 ± 0.33	0.619	1.37 ± 0.30	1.35 ± 0.34	0.584	0.940
LDL (mmol/L)	2.86 ± 0.87	2.61 ± 0.72	0.051	3.10 ± 0.86	2.80 ± 0.79	0.011	0.919
Triglyceride (mmol/L)	1.08 ± 0.41	1.10 ± 0.42	0.849	1.08 ± 0.41	1.06 ± 0.46	0.572	0.671

[a]*p*-value for paired sample *t*-test pre- to post- intervention.

[b]*p*-value for paired *t*-test pre- to post- control condition.

[c]ANCOVA *p*-values for intervention effects controlled for baseline values.

Abbreviations: 24 h BP, averaged 24-h blood pressure measured every 20 min; BMI, body mass index; dia, diastolic; HDL, high density lipoprotein; Hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; Max. Watt, maximal power output; Rest. BP, blood pressure after 10 min. of rest in a lying position; SD, standard deviation; Stress BP, blood pressure measured directly after cardiopulmonary exercise stress test; sys, systolic; $\dot{V}O_2$ peak, peak oxygen uptake.

mortality rates. However, our data showed that DVA may be of value allowing for early distinction between vascular responders and non-responders in response to an add-on exercise treatment in patients with hypertension. Timely detection of non-responder on a vascular level may allow for better clinical decision-making, such as therapy modification, resulting in possibly better outcome in vascular diseases such as stroke or myocardial infarction. However, exercise intervention studies demonstrating that improving retinal microvascular function is related to better CV outcome are still lacking.

Evidence exists that exercise training can improve FMD in different patient cohorts.[45–48] All of these studies trained for more than 8 weeks. A recent meta-analysis showed that especially intervention spans of more than 10 weeks seemed beneficial for detecting improvements in FMD.[49] In addition, Moriguchi et al showed that FMD improvements after 12 weeks exercise training were associated with blood pressure reductions.[50] The HIIT group in our study showed no blood pressure changes after the intervention phase. We would like to speculate that the short intervention period of 8 weeks in combination with the lack of blood pressure reduction might be responsible for the absence of improvements in macrovascular endothelial function in our study.

A previous study found CRF to be an important mediator of improvements in endothelial function of the microcirculation.[44] Interestingly, exercise-induced improvements of aFID were independent of age, sex and changes in CRF, blood pressure or BMI. Arteriolar FID seems to be an independent and sensitive vascular biomarker to detect beneficial exercise-induced effects on microvascular endothelial function. Especially, aFID has been shown to be predictive for CV outcome in patients

TABLE 2 Vascular biomarkers in patients with hypertension before and after exercise or control condition.

	Intervention group ($n = 19$) Mean ± SD			Control group ($n = 19$) Mean ± SD			
	Pre	Post	p^a	Pre	Post	p^b	p^c
FMD (%)	4.90 ± 2.35	4.99 ± 2.01	0.840	4.35 ± 1.31	4.31 ± 1.15	0.881	0.384
FMD Baseline Dia. (mm)	4.14 ± 0.62	3.76 ± 1.55	0.253	3.80 ± 1.21	4.02 ± 0.85	0.231	0.187
FMD max. Dia. (mm)	4.32 ± 0.62	4.41 ± 0.84	0.381	4.15 ± 0.83	4.19 ± 0.86	0.582	0.757
FMD rest. Dia. (mm)	4.15 ± 0.62	4.18 ± 0.80	0.709	4.02 ± 0.80	4.05 ± 0.93	0.683	0.855
FMD max. range (mm)	0.17 ± 0.09	0.23 ± 0.20	0.120	0.13 ± 0.11	0.14 ± 0.20	0.943	0.153
aFID (%)	2.40 ± 0.98	3.19 ± 1.31	<0.001	3.06 ± 1.50	2.90 ± 1.46	0.280	<0.001
vFID (%)	3.65 ± 1.41	3.58 ± 1.14	0.793	3.71 ± 1.42	3.50 ± 1.25	0.237	0.660
aCON (%)	−1.93 ± 1.53	−2.29 ± 1.7	0.226	−1.24 ± 1.41	−1.71 ± 1.35	0.080	0.821

[a]*p*-value for paired sample *t*-test pre- to post- intervention.

[b]*p*-value for paired *t*-test pre- to post- control condition.

[c]ANCOVA *p*-values for intervention effects controlled for baseline values.

Abbreviations: aCON, arteriolar constriction after flicker light; aFID, arteriolar flicker light-induced dilation; FMD Baseline Dia., baseline diameter; FMD max. Dia., maximal diameter; FMD max. range., maximal range; FMD rest. Dia., resting diameter; FMD, flow-mediated dilation; SD, standard deviation; vFID, venular flicker light-induced dilation.

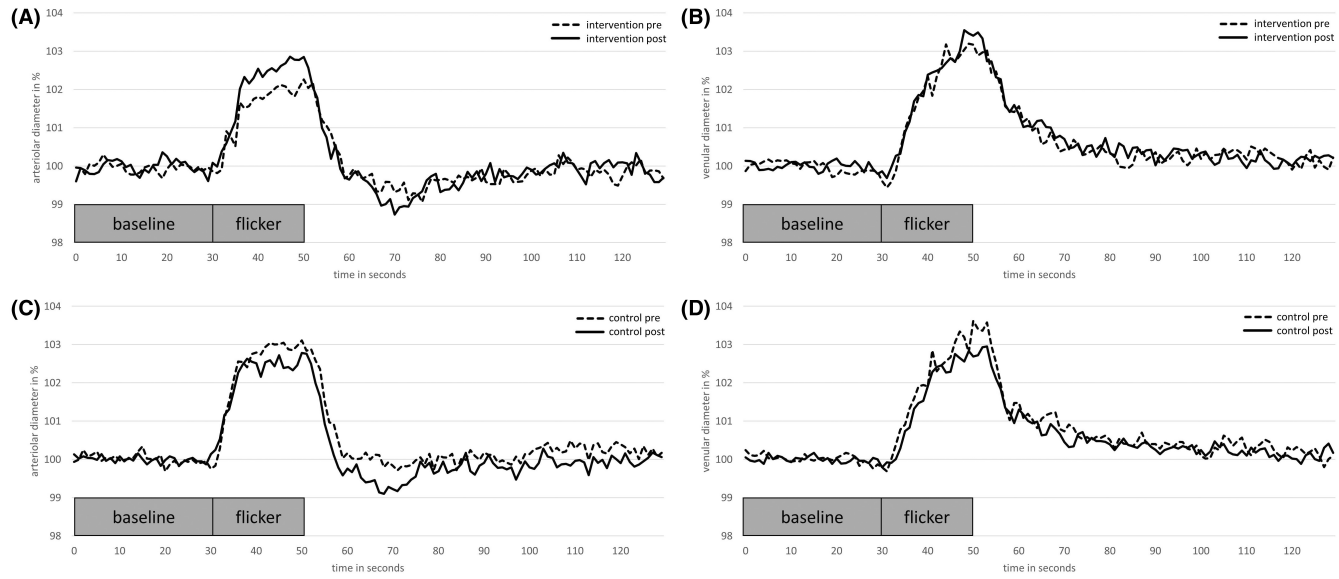

FIGURE 2 Median flicker response curves. Median flicker light-induced response curves for arterioles (A) and venules (B) of the high-intensity interval training group and for arterioles (C) and venules (D) of the control group before (pre) and after (post) 8 weeks of intervention.

with CV diseases.[15] Exercise-induced increase in aFID can therefore be seen as a surrogate biomarker for CV risk reduction and improvement of CV outcome in patients with hypertension. It also appears plausible from a pathophysiological point of view that endothelial microvascular function of resistance vessels, being the key determinants of peripheral blood pressure regulation, is most sensitively affected by hemodynamic stimuli such as shear stress as compared to large arteries in patients with hypertension. Venular retinal dilatation was not affected by exercise training. Wall shear stress has been shown to be greater in arterioles than in post-capillary venular vessels.[51] Exercise-induced shear stress is thought to be buffered by the arteriolar and capillary system. Additionally, venular vessel structure differs from arteriolar structure in the extent of their smooth muscle cell layer leaving venular vessels as a more passive structure of the microcirculation.

It remains to be discussed that the current PA recommendations did not improve CRF and vascular health. The current guidelines seem to be insufficient with respect to

TABLE 3 Linear regression models.

	aFID		FMD	
Model	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***
HIIT vs. control				
1	0.87 (0.39–1.34)	<0.001	0.48 (−0.40–1.37)	0.274
2	0.83 (0.34–1.32)	0.002	0.34 (−0.61–1.28)	0.472
3	0.92 (0.36–1.48)	0.002	0.52 (−0.60–1.63)	0.351
4	0.92 (0.34–1.50)	0.003	0.50 (−0.66–1.65)	0.386

Abbreviations: aFID, arteriolar flicker light-induced dilation; FMD, flow-mediated dilation; HIIT, high-intensity interval training; Model 1, adjusted for age, sex and antihypertensive medication at baseline; Model 2, adjusted for age, sex, antihypertensive medication at baseline, Δsys. and Δdia. blood pressure; Model 3, adjusted for age, sex, antihypertensive medication at baseline, Δsys. and Δdia. blood pressure and $\Delta\dot{V}O_2$peak; Model 4, adjusted for age, sex, antihypertensive medication at baseline, Δsys. and Δdia. blood pressure, $\Delta\dot{V}O_2$peak and Δbody mass index; *p*, level of significance of the regression models.

their ability of improving those parameters in a short-term setting of 8 weeks. This study shows proof of concept for exercise and retinal endothelial function. Future studies will have to verify volume and intensity necessary to achieve clinically relevant effects on microvascular and macrovascular function. A diameter increase of less than 1% relative to baseline in response to flicker light may appear small; however, it lies within the range that distinguishes healthy from disease older adults.[20,23]

Moreover, future studies have to investigate whether patients without vascular adaptation to short-term exercise, termed non-responders, may benefit from increases in exercise duration and volume and respond to intensified exercise treatment. This may allow for retinal vessel analysis to be used as a treatment monitoring tool to support decision-making in clinical practice, both with respect to exercise treatment and drug treatment.

4.2 | Effects of exercise therapy on blood pressure and cardiovascular risk factors

Similar effects of HIIT on body composition and $\dot{V}O_2$peak as found in the present study were found previously in patients at CV risk[44] but were now confirmed in patients with arterial hypertension in a shorter time frame of 8 weeks. Low muscle strength was previously associated with elevated risk of all-cause mortality.[52] In our study, maximal power output during the bicycle ramp protocol was significantly increased in the HIIT group, which may further imply that the risk of all-cause mortality was likely reduced in the intervention group. No changes in blood pressure were observed in the intervention group. However, evidence exists that regular physical activity and exercise interventions both have strong blood pressure lowering effects[53] and are associated with reduced CV and all-cause mortality in hypertensive patients in general.[54] Cornelissen and Smart highlighted in their meta-analysis that especially male subjects seem to benefit from exercise interventions to lower their blood pressure levels. In addition, interventions with high intensities seem to be more effective in blood pressure reduction compared to low training intensities.[53] A recent published consensus document from the European Association of Preventive Cardiology and the ESC Council on Hypertension discussed the lack of exercise guidelines for HIIT in hypertensive patients with high CV risk to avoid overtraining. This research gap has to be addressed in future studies. Participants in our study performed an exercise intervention with high intensities (80–95% HRmax) but only for 8 weeks. We would like to speculate that a longer training period might have blood pressure lowering effects in hypertensive patients but has to be periodized adequately to avoid overtraining. Interestingly, changes in microvascular function were independent of changes in BP and occur before BP-lowering effects of exercise can be detected. For the investigated blood markers, a decrease in fasted blood glucose was observed. As a marker of systemic inflammation, hs-CRP was investigated to detect expected anti-inflammatory exercise effects.[55] However, due to the low baseline levels of hs-CRP, no significant changes were observed after HIIT.

4.3 | Limitations

This study examined the effects of an eight-week exercise intervention on endothelial function, blood pressure, CRF, and body composition in patients with hypertension. We aimed at a short-term exercise exposure to assess the sensitivity and validity of retinal microvascular and brachial large artery endothelial function in response to the treatment stimulus. Retinal aFID appears to be a more sensitive and valid biomarker to detect short-term exercise effects and may therefore be used as monitoring tool to quantify treatment efficacy. It remains to be shown which exercise duration and volumes are necessary to improve large artery function and wall properties. It is also likely that longer exercise duration and volume will have even stronger effects on retinal aFID than those observed in this study. Also, it must be noted that the present study was conducted with a specific subpopulation and can subsequently not per se be generalized to younger, healthy or other disease populations. Moreover, a comparison between HIIT and other training methods regarding their ability to improve endothelial function would be of scientific and clinical interest. Long-term prospective follow-up studies are required to reveal the

full potential of vascular assessments in CV risk stratification and CV outcome.

5 | CONCLUSION AND PERSPECTIVE

Short-term HIIT is effective in improving retinal microvascular but not brachial large artery endothelial function in patients with hypertension. Retinal aFID may prove to be a sensitive biomarker to quantify exercise treatment efficacy in patients with hypertension at the microvascular level and at short time intervals. Future studies need to investigate whether dynamic retinal vessel imaging may be applied as a treatment monitoring tool of exercise treatment, and potentially drug treatment, in hypertension with perspective to support clinical decision-making in clinical practice.

AUTHORS' CONTRIBUTIONS

ST led the intervention, took part in the data acquisition and analysis, and wrote the manuscript. CH supported the data collection. JG, JC, and TH were responsible for clinical examinations. KG was the ophthalmologist in this study and supported the investigators in diagnosing local eye diseases as exclusion criteria. AST provided expertise in macrovascular assessments. HH designed the study and provided clinical and academic expertise. LS was the PI of this study, designed the study, and was responsible for micro- and macrovascular assessments and the intervention. All authors revised the manuscript, approved the final version of the manuscript, and agreed with the order of presentation of the authors.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT

All patients singed a written informed consent prior the first assessment.

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REFERENCES

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7
2. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1923-1994. doi:10.1016/S0140-6736(18)32225-6
3. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet*. 2020;395(10226):795-808. doi:10.1016/S0140-6736(19)32008-2
4. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16(4):223-237. doi:10.1038/s41581-019-0244-2
5. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol*. 2021;28:1-18. doi:10.1038/s41569-021-00559-8
6. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9
7. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365(9455):217-223. doi:10.1016/S0140-6736(05)17741-1
8. Nowak KL, Rossman MJ, Chonchol M, Seals DR. Strategies for achieving healthy vascular aging. *Hypertension*. 2018;71(3):389-402. doi:10.1161/HYPERTENSIONAHA.117.10439
9. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990 s. *Nature*. 1993;362(6423):801-809. doi:10.1038/362801a0
10. Thijssen DHJ, Bruno RM, van Mil ACCM, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J*. 2019;40(30):2534-2547. doi:10.1093/eurheartj/ehz350

11. Xu Y, Arora RC, Hiebert BM, et al. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2014;15(7):736-746. doi:10.1093/ehjci/jet256
12. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. *J Am Heart Assoc*. 2015;4(11):e002270. doi:10.1161/JAHA.115.002270
13. Yang Y, Xu JZ, Wang Y, Tang XF, Gao PJ. Brachial flow-mediated dilation predicts subclinical target organ damage progression in essential hypertensive patients: a 3-year follow-up study. *J Hypertens*. 2014;32(12):2393-2400; discussion 2400. doi:10.1097/HJH.0000000000000337
14. Günthner R, Hanssen H, Hauser C, et al. Impaired retinal vessel dilation predicts mortality in end-stage renal disease. *Circ Res*. 2019;124:1796-1807. doi:10.1161/CIRCRESAHA.118.314318
15. Theuerle JD, Al-Fiadh AH, Amirul Islam FM, et al. Impaired retinal microvascular function predicts long-term adverse events in patients with cardiovascular disease. *Cardiovasc Res*. 2021;117(8):1949-1957. doi:10.1093/cvr/cvaa245
16. Günthner R, Streese L, Angermann S, et al. Mortality prediction of retinal vessel diameters and function in a long-term follow-up of haemodialysis patients. *Cardiovasc Res*. 2022;118(16):3239-3249. doi:10.1093/cvr/cvac073
17. Machalińska A, Pius-Sadowska E, Babiak K, et al. Correlation between flicker-induced retinal vessel vasodilatation and plasma biomarkers of endothelial dysfunction in hypertensive patients. *Curr Eye Res*. 2018;43(1):128-134. doi:10.1080/02713683.2017.1358372
18. Kotliar KE, Lanzl IM, Schmidt-Trucksäss A, et al. Dynamic retinal vessel response to flicker in obesity: a methodological approach. *Microvasc Res*. 2011;81(1):123-128. doi:10.1016/j.mvr.2010.11.007
19. Patel SR, Bellary S, Karimzad S, Gherghel D. Overweight status is associated with extensive signs of microvascular dysfunction and cardiovascular risk. *Sci Rep*. 2016;6:32282. doi:10.1038/srep32282
20. Nägele MP, Barthelmes J, Ludovici V, et al. Retinal microvascular dysfunction in hypercholesterolemia. *J Clin Lipidol*. 2018;12(6):1523-1531.e2. doi:10.1016/j.jacl.2018.07.015
21. Seshadri S, Ekart A, Gherghel D. Ageing effect on flicker-induced diameter changes in retinal microvessels of healthy individuals. *Acta Ophthalmol*. 2016;94(1):e35-e42. doi:10.1111/aos.12786
22. Sörensen BM, Houben AJHM, Berendschot TTJM, et al. Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: the Maastricht study. *Circulation*. 2016;134(18):1339-1352. doi:10.1161/CIRCULATIONAHA.116.023446
23. Nägele MP, Barthelmes J, Ludovici V, et al. Retinal microvascular dysfunction in heart failure. *Eur Heart J*. 2018;39(1):47-56. doi:10.1093/eurheartj/ehx565
24. Streese L, Lona G, Wagner J, et al. Normative data and standard operating procedures for static and dynamic retinal vessel analysis as biomarker for cardiovascular risk. *Sci Rep*. 2021;11(1):14136. doi:10.1038/s41598-021-93617-7
25. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104. doi:10.1093/eurheartj/ehy339
26. Vatten LJ, Nilsen TIL, Holmen J. Combined effect of blood pressure and physical activity on cardiovascular mortality. *J Hypertens*. 2006;24(10):1939-1946. doi:10.1097/01.hjh.0000244941.49793.f9
27. Huai P, Xun H, Reilly KH, Wang Y, Ma W, Xi B. Physical activity and risk of hypertension: a meta-analysis of prospective cohort studies. *Hypertension*. 2013;62(6):1021-1026. doi:10.1161/HYPERTENSIONAHA.113.01965
28. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699. doi:10.1161/CIR.0000000000000461
29. Kachur S, Chongthammakun V, Lavie CJ, et al. Impact of cardiac rehabilitation and exercise training programs in coronary heart disease. *Prog Cardiovasc Dis*. 2017;60(1):103-114. doi:10.1016/j.pcad.2017.07.002
30. Kondamudi N, Haykowsky M, Forman DE, Berry JD, Pandey A. Exercise training for prevention and treatment of heart failure. *Prog Cardiovasc Dis*. 2017;60(1):115-120. doi:10.1016/j.pcad.2017.07.001
31. Hanssen H, Boardman H, Deiseroth A, et al. Personalized exercise prescription in the prevention and treatment of arterial hypertension: a consensus document from the European Association of Preventive Cardiology (EAPC) and the ESC Council on hypertension. *Eur J Prev Cardiol*. 2022;29:205-215. doi:10.1093/eurjpc/zwaa141
32. Konukoglu D, Uzun H. Endothelial dysfunction and hypertension. *Adv Exp Med Biol*. 2017;956:511-540.
33. Dharmashankar K, Widlansky ME. Vascular endothelial function and hypertension: insights and directions. *Curr Hypertens Rep*. 2010;12:448-455.
34. Benjamin EJ, Larson MG, Keyes MJ, et al. Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham heart study. *Circulation*. 2004;109:613-619.
35. Streese L, Gander J, Carrard J, et al. Hypertension and retinal microvascular dysfunction (HyperVasc): protocol of a randomised controlled exercise trial in patients with hypertension. *BMJ Open*. 2022;12(6):e058997. doi:10.1136/bmjopen-2021-058997
36. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053
37. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the atherosclerosis risk in communities study. *Ophthalmology*. 1999;106(12):2269-2280. doi:10.1016/s0161-6420(99)90525-0
38. Riva CE, Logean E, Falsini B. Visually evoked hemodynamical response and assessment of neurovascular coupling in the optic nerve and retina. *Prog Retin Eye Res*. 2005;24(2):183-215. doi:10.1016/j.preteyeres.2004.07.002
39. Pemp B, Weigert G, Karl K, et al. Correlation of flicker-induced and flow-mediated vasodilatation in patients with endothelial dysfunction and healthy volunteers. *Diabetes Care*. 2009;32(8):1536-1541. doi:10.2337/dc08-2130
40. Anderson LJ, Erceg DN, Schroeder ET. Utility of multifrequency bioelectrical impedance compared with dual-energy x-ray absorptiometry for assessment of total and regional body composition varies between men and women. *Nutr Res N Y N*. 2012;32(7):479-485. doi:10.1016/j.nutres.2012.05.009

41. Wagner J, Knaier R, Infanger D, et al. Functional aging in health and heart failure: the COmPLETE study. *BMC Cardiovasc Disord*. 2019;19(1):180. doi:10.1186/s12872-019-1164-6
42. Wagner J, Niemeyer M, Infanger D, et al. New data-based cutoffs for maximal exercise criteria across the lifespan. *Med Sci Sports Exerc*. 2020;52(9):1915-1923. doi:10.1249/MSS.0000000000002344
43. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and Other Societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106
44. Streese L, Kotliar K, Deiseroth A, et al. Retinal endothelial function in cardiovascular risk patients: a randomized controlled exercise trial. *Scand J Med Sci Sports*. 2020;30(2):272-280. doi:10.1111/sms.13560
45. Molmen-Hansen HE, Stolen T, Tjonna AE, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol*. 2012;19(2):151-160. doi:10.1177/1741826711400512
46. Ghardashi Afousi A, Izadi MR, Rakhshan K, Mafi F, Biglari S, Gandomkar BH. Improved brachial artery shear patterns and increased flow-mediated dilatation after low-volume high-intensity interval training in type 2 diabetes. *Exp Physiol*. 2018;103(9):1264-1276. doi:10.1113/EP087005
47. Areas GPT, Mazzuco A, Caruso FR, et al. Flow-mediated dilation and heart failure: a review with implications to physical rehabilitation. *Heart Fail Rev*. 2019;24(1):69-80. doi:10.1007/s10741-018-9719-7
48. Son Y, Kim K, Jeon S, Kang M, Lee S, Park Y. Effect of exercise intervention on flow-mediated dilation in overweight and obese adults: meta-analysis. *Int J Vasc Med*. 2017;2017:7532702-7532711. doi:10.1155/2017/7532702
49. Mattioni Maturana F, Martus P, Zipfel S, NIEß AM. Effectiveness of HIIE versus MICT in improving cardiometabolic risk factors in health and disease: a meta-analysis. *Med Sci Sports Exerc*. 2021;53(3):559-573. doi:10.1249/MSS.0000000000002506
50. Moriguchi J, Itoh H, Harada S, et al. Low frequency regular exercise improves flow-mediated dilatation of subjects with mild hypertension. *Hypertens Res off J Jpn Soc Hypertens*. 2005;28(4):315-321. doi:10.1291/hypres.28.315
51. Nagaoka T, Yoshida A. Noninvasive evaluation of wall shear stress on retinal microcirculation in humans. *Invest Ophthalmol Vis Sci*. 2006;47(3):1113-1119. doi:10.1167/iovs.05-0218
52. Li R, Xia J, Zhang X, et al. Associations of muscle mass and strength with all-cause mortality among US older adults. *Med Sci Sports Exerc*. 2018;50(3):458-467. doi:10.1249/MSS.0000000000001448
53. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2(1):e004473. doi:10.1161/JAHA.112.004473
54. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. *J Hypertens*. 2012;30(7):1277-1288. doi:10.1097/HJH.0b013e3283544669
55. Lavie CJ, Arena R, Swift DL, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. *Circ Res*. 2015;117(2):207-219. doi:10.1161/CIRCRESAHA.117.305205

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