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ORIGINAL RESEARCH ARTICLE

Hypertrophic remodelling of retinal arterioles in patients with congestive heart failure

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Abstract

Aims Analysis of microvascular parameters in the retinal circulation—known to reflect those in the systemic circulation—allows us to differentiate between eutrophic and hypertrophic remodelling of small arteries. This study aimed to examine microvascular changes in patients with congestive heart failure (CHF) and reduced as well as mid-range ejection fraction.

Methods and results Forty subjects with CHF underwent measurement of retinal capillary flow (RCF), wall-to-lumen ratio (WLR), vessel and lumen diameter, wall thickness, and wall cross-sectional area (WCSA) of retinal arterioles of the right eye by scanning laser Doppler flowmetry (SLDF). Applying a matched pair approach, we compared this group with reference values of age-matched controls from a random sample in the population of Pilsen, Czech Republic. There was no significant difference in RCF and WLR between the groups (RCF: $P = 0.513$; WLR: $P = 0.106$). In contrast, wall thickness and WCSA, indicators of hypertrophic remodelling, were higher in CHF subjects (WT: 15.0 ± 4.2 vs. 12.7 ± 4.2 μm, $P = 0.021$; WCSA: 4437.6 ± 1314.5 vs. 3615.9 ± 1567.8 μm^2, $P = 0.014$). Similarly, vessel (109.4 ± 11.1 vs. 100.5 ± 14.4 μm, P = 0.002) and lumen diameter (79.0 ± 7.9 vs. 75.2 ± 8.5 μm, P = 0.009) were increased in CHF.

Conclusions In CHF subjects, we observed hypertrophic remodelling of retinal arterioles indicative of similar changes of small resistance arteries in the systemic circulation. Microvascular structure and function assessed by SLDF may thereby represent a useful, non-invasive method for monitoring of microvascular damage in patients with CHF and may offer innovative treatment targets for new CHF therapies.

Keywords Hypertrophic remodelling; Retina; Heart failure; Microvasculature

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Introduction

Microvascular changes, such as eutrophic or hypertrophic remodelling, represent one of the first manifestations of target organ damage in a variety of diseases, such as hypertension,[1–4] type 2 diabetes mellitus (T2DM),[5–8] cardiovascular,[9–11] and even cerebrovascular disease.[12–15] In hypertension, for example, they may even occur prior to cardiac hypertrophy or proteinuria, and microvascular remodelling has repeatedly been shown to have prognostic significance with respect to major cardiovascular events and mortality.[1,9,14,16–20]

Invasive evaluation of the microcirculation can be and has been performed *ex vivo* by means of biopsies of subcutaneous arterioles.[5,7] However, non-invasive methods for *in vivo* evaluation of the microcirculatory state are scarce. The retinal microcirculation represents an attractive option that can be visualized and precisely analysed by scanning laser Doppler flowmetry (SLDF).[21,22]

Scanning laser Doppler flowmetry represents a reliable, non-invasive, and safe method to assess retinal microcirculation *in vivo* and has been developed and frequently performed in our and other clinical research centres[12,22–24] in contrast to the adaptive optics methodology.[25] This

technique allows us to determine retinal perfusion, that is retinal capillary flow (RCF) as well as structural parameters such as wall thickness, vessel and lumen diameter, wall-to-lumen ratio (WLR), and wall cross-sectional area (WCSA) of retinal arterioles.[26]

In subjects without congestive heart failure (CHF), we found eutrophic vascular remodelling in mildly to moderately hypertensive patients.[2] In order to protect the vessel wall from elevated blood pressure (BP), hypertension induces a rearrangement of smooth muscle cells leading to an increase in WLR but not necessarily to a vascular hypertrophic response indicated by an increase in WCSA.[1,2,4,20,27] In contrast, hypertrophic vascular remodelling was found in subjects with T2DM, predominantly consisting of a vascular growth response, which leads to an increase in both WLR and WCSA.[5–8]

Vascular dysfunction has been previously shown to play a central role in the pathophysiology of CHF.[28,29] Especially macrovascular dysfunction has been frequently described as indicator for hospitalization rate, adverse outcome, and even mortality in subjects with CHF and other cardiovascular diseases.[30,31] Microvascular structure and function are important surrogate parameters for macrovascular damage and may thereby represent a useful method for monitoring of microvascular damage in CHF in patients and may represent innovative treatment targets for new CHF therapies. However, non-invasive, simple methods for the evaluation of microvascular alterations are limited. In light of these considerations, precise examination of microvascular alterations of the retina by means of S represents an attractive diagnostic tool. In this study, we compared retinal microvascular alterations in subjects with CHF and reduced as well as mid-range left ventricular ejection fraction (LVEF) to healthy controls by means of SLDF.

Methods

Study design

Within a randomized, double-blind, placebo-controlled, parallel-group clinical trial that evaluates sodium imbalance and vascular changes in patients with CHF and reduced as well as mid-range LVEF (ClinicalTrials.gov Identifier: NCT03128528), subjects underwent SLDF measurement at the Clinical Research Center of the Department of Nephrology and Hypertension, University Hospital Erlangen-Nuremberg, Germany (http://www.crc-erlangen.de) between July 2017 and 2019.

Study participants were recruited from the university clinics, by means of local newspaper advertisement and referring physicians. Written informed consent was obtained from each subject before study inclusion. The study was conducted according to the tenets of the Declaration of Helsinki and the principles of good clinical practice guidelines. The study protocol has been approved by the local Ethics Committee of the University of Erlangen-Nuremberg.

This cohort of CHF patients was compared with age-matched controls obtained from the Czech post-MONICA (MONItoring trends and determinants in CArdiovascular disease) auxiliary study, aiming to establish reference values for functional and structural parameters of retinal microcirculation by means of SLDF, including a total of 256 apparently healthy individuals from an urban random population sample of Pilsen, Czech Republic. The Czech post-MONICA study was approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital, Prague, Czech Republic. All participants signed informed consent.[32]

Study population

Cases

The group of subjects with CHF consisted of n = 40 individuals and was defined according to the European Guidelines for the diagnosis and treatment of acute and chronic heart failure.[33] Subjects were included if their LVEF was below 40% and they had symptoms and/or signs of CHF or if their LVEF was 40–49% and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values above 125 pg/mL and evidence of relevant structural heart disease such as left ventricular hypertrophy or atrial enlargement and/or diastolic dysfunction. Key exclusion criteria were acute cardiac decompensation, dyspnoea at rest, uncontrolled arterial hypertension ($>$180/110 mmHg), uncontrolled diabetes (fasting plasma glucose $\geq$ 240 mg/dL, glycated haemoglobin $\geq$ 10%), any history of stroke, transient ischemic attack, instable angina pectoris, or myocardial infarction within the last 6 months prior to study inclusion and eye diseases such as cataract, glaucoma, age-related macular degeneration, or diabetic as well as hypertensive retinopathy. Other main exclusion criteria were an estimated glomerular filtration rate below 30 mL/min/1.73 m^2 and a body mass index higher than 40 kg/m^2 or active smoking status (ClinicalTrials.gov NCT03128528).

Controls

The control group consisted of 40 individuals from the Czech post-MONICA study. In this study, a total of 398 randomly selected individuals from an urban population aged 25 to 65 years, resident in Pilsen, Czech Republic, underwent a screening for major cardiovascular risk factors. Our SLDF echnology was applied for the assessment of retinal microcirculation. Complete data on retinal microcirculation were available for 256 individuals free from manifest cardiovascular disease, diabetes, and drug treatment for hypertension and/or dyslipidaemia. From this group, a total of

40 age-matched individuals were included into the current analysis and used as controls. The protocol for the assessment of retinal parameters as well as the staff performing and analysing the measurements were the same in both the groups.[32]

Clinical parameters

Cases

Demographic data of all participants including medical history and concomitant medication were assessed. In the group of subjects with CHF, fasting blood samples were obtained to measure NT-proBNP in the group of subjects with CHF, creatinine, fasting plasma glucose, and glycated haemoglobin. Assessment of office BP and heart rate was carried out in standard fashion by validated devices (DINAMAP® PRO 100V2, GE Critikon) in a seated position after 5 min of rest according to European Society of Cardiology/European Society of Hypertension guideline recommendations.[34]

Controls

The screening examination consisted of a physician-completed questionnaire; currently prescribed drugs were recorded and verified (if possible) against drug containers. A gentle venous blood sampling was performed in the sitting position after at least a 12-h fast. The obtained samples were centrifuged at 1500*g* and frozen thereafter. Height and body weight were measured, BP measurement was performed consistently on the right arm (supported at the heart level), in the sitting position, after at least a 5-min rest. Three consecutive BP measurements were obtained using standard mercury sphygmomanometers (Baumanometer; W.A. Baum Co. Inc., New York, New York, USA) and correctly sized cuffs. BP values were recorded to the nearest 2 mmHg. The mean value of the last two readings was used for the analyses.[32]

Retinal parameters

In each subject, SLDF at a wavelength of 670 nm (Heidelberg Retina Flowmeter, Heidelberg Engineering, Germany) was performed to determine RCF, WLR, vessel and lumen diameter, wall thickness, and WCSA of retinal arterioles of the right eye.[12,22] In addition to baseline mean, systolic, and diastolic RCF values, pulsed RCF was determined in order to analyse the pulsatile component of the vascular system. Measurements of the CHF group were performed at the Clinical Research Center of the Department of Nephrology and Hypertension, University Hospital Erlangen-Nuremberg, Germany, and measurements of the control group were performed in Pilsen, Czech Republic. Three measurements of each subject were taken after 15 min of rest in sitting position by the same group of experienced investigators in a dark, temperature-controlled room in the morning. Subjects were fasting since the evening before the examination and instructed not to perform training the day before examination. With mydriatic agents such as tropicamide being known to affect correct measurement of retinal microcirculatory parameters,[22,35] is noteworthy to mention that no pupil dilation was applied for the examination. Measurements were taken in the juxtapapillary area, 2- to 3-mm temporal superior of the optic nerve.

Analyses of diameters were performed offline with automatic fullfield perfusion imaging analysis.[36–38] Vessel diameter was measured in reflection images and lumen diameter in perfusion images. Wall thickness was calculated using the formula vessel diameter − lumen diameter / 2, and WCSA was calculated using the formula $(\pi/4) \times$ (vessel diameter^2 − lumen diameter^2). WLR was calculated using the formula (vessel diameter − lumen diameter)/lumen diameter.[12]

Each image was analysed by experienced technicians, supervised and in case of discrepancy finally validated by the most experienced scientist (J.H.) of the group to assure uniform and correct data acquisition. Data were calculated as mean values of the three images. Further quality control data such as variation coefficients and inter-reader-variability as well as intra-reader-variability of the SLDF method are given in previous studies from our research group.[12,22] Briefly, interobserver and intraobserver reliability did not differ across various investigators and patient groups and showed in nearly all circumstances coefficients of variations of less than 10%, except of wall cross-sectional area (12.5%).

Statistical analysis

All analyses were performed using SPSS software, Version 21.0 (IBM Corporation, Chicago, IL, USA). Data are expressed as mean ± standard deviation or median and 95% confidence interval depending on data distribution. A two-sided P value < 0.05 was considered statistically significant. Applying a matched-pair approach, each subject with CHF was compared with an age-matched subject from the control group. Subsequently, paired *t*-test and Wilcoxon-test were applied for comparison of retinal microvascular parameters between the two groups.

Results

Clinical characteristics

Table 1 provides the clinical characteristics of the two study cohorts. The average age in the CHF group was 64 ± 7 years. $N = 32$ subjects were male (80%) and $n = 8$ subjects were female (20%). Mean body mass index was 29 ± 4 kg/m^2.

Table 1 Clinical characteristics of the study population

Parameter	CHF group (n = 40)	Control group (n = 40)[32]	P value
Age (years)	64 ± 7	62 ± 2	0.150
Gender male/female (%)	80/20	45/55	0.025
Systolic BP (mmHg)	122 ± 16	130 ± 21	0.072
Diastolic BP (mmHg)	74 ± 11	86 ± 11	<0.001
PP (mmHg)	48 ± 12	45 ± 13	0.201
HR (bpm)	63 ± 10	68 ± 9	0.029
Aetiology (%) ICM	67	—	—
DCM	23		
Other	10		
LVEF (%)	39 ± 7	—	—
NT-proBNP (pg/mL)	717 ± 705	—	—
Hypertension (%)	75	0	—
T2DM (%)	15	0	—

Data are given as mean ± standard deviation.
BP, blood pressure; CHF, congestive heart failure; DCM, dilated cardiomyopathy; HR, heart rate; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PP, pulse pressure; T2DM, type 2 diabetes mellitus.

Office BP was 122 ± 16/74 ± 11 mmHg, and pulse pressure (PP) 48 ± 12 mmHg with a heart rate of 62 ± 10 bpm.

In the CHF group, 67% of subjects suffered from ischemic cardiomyopathy (n = 27), 23% from dilated cardiomyopathy (n = 9), and 10% from other forms of cardiomyopathy (n = 4). Mean LVEF was 39 ± 7%, and mean NT-proBNP was 717 ± 705 pg/mL. A total of 75% (n = 30) of subjects had arterial hypertension and 15% (n = 6) T2DM.

With an average age of 62 ± 2 years, the age in the control group did not differ significantly from the CHF group (P = 0.150), thus matching for age was successful. BP was significantly higher in the control group than in the CHF group (130 ± 21/86 ± 11 mmHg, P = 0.072 and $P < 0.001$, respectively). PP did not differ significantly between the two groups (45 ± 13 mmHg, P = 0.201). None of the patients had hypertension, T2DM, or any cardiac disease, in particular with no clinical symptoms or signs of CHF.[32]

Retinal parameters

Table 2 shows a comparison of retinal parameters between subjects with CHF and controls. Mean RCF did not differ significantly between subjects with CHF (287.4 ± 74.6 AU) and controls (303.2 ± 108.5 AU, P = 0.513). Similarly, neither systolic (CHF: 412.2 ± 87.5 AU, controls: 409.1 ± 115.5 AU) nor diastolic RCF (CHF: 190.6 ± 71.4 AU, controls: 221.5 ± 109.6 AU) were significantly different between the two groups (P = 0.904 and P = 0.187, respectively). In contrast, pulsed RCF was higher in the CHF group (221.6 ± 74.9 AU) compared with controls (187.6 ± 40.5 AU, P = 0.020).

Wall-to-lumen ratio did not differ significantly between subjects with CHF (0.373 ± 0.10) and controls (0.335 ± 0.98, P = 0.106). Vessel diameter was higher in the CHF group (109.4 ± 11.1 μm) compared with controls (100.5 ± 14.4 μm, P = 0.002) as was lumen diameter (CHF: 79.9 ± 7.9 μm, controls: 75.2 ± 8.5 μm, P = 0.009). Wall thickness was higher in subjects with CHF (15.0 ± 4.2 μm) compared with the control group (12.7 ± 4.2 μm, P = 0.021). Similarly, WCSA was higher in the CHF group (4437.6 ± 1314.5 μm) in comparison with controls (3615.9 ± 1567.8 μm, P = 0.014, *Figure 1*).

Discussion

In the current study, we analysed retinal structural and functional parameters in subjects with CHF compared with controls taken from an epidemiological health examination. We observed greater values for vessel diameter, lumen diameter, wall thickness, and WCSA in the group of subjects with CHF than in controls indicative of hypertrophic vascular alterations in CHF.

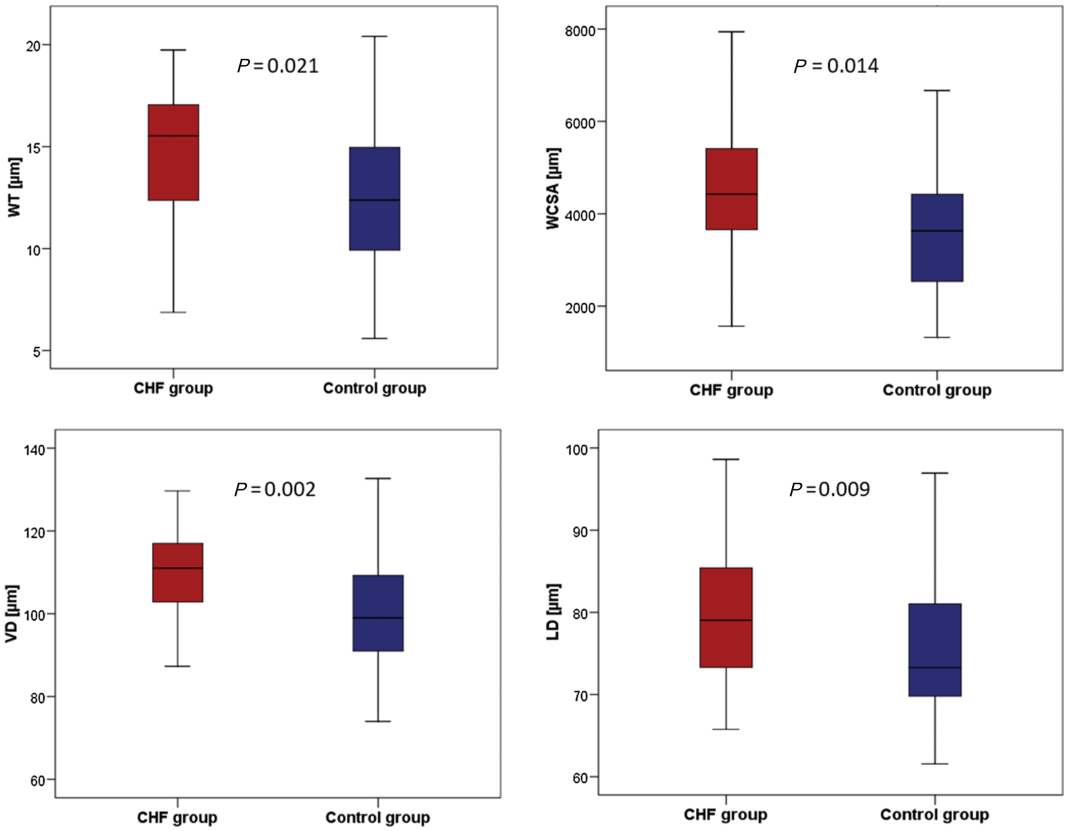
In the literature, two forms of arteriolar alterations have been described, namely vascular remodelling and vascular growth.[2] In subjects with mild to moderate hypertension, mechano-adaptive processes protect the vessel wall from

Table 2 Comparison of retinal parameters between subjects with CHF and controls

Parameter	CHF group (n = 40)	Control group (n = 40)[39]	P value
Retinal capillary perfusion			
RCF mean (AU)	287.4 ± 74.6	303.2 ± 108.5	0.513
RCF sys (AU)	412.2 ± 87.5	409.1 ± 115.5	0.904
RCF dia (AU)	190.6 ± 71.4	221.5 ± 109.6	0.187
RCF pulsed (AU)	221.6 ± 74.9	187.6 ± 40.5	0.020
Structural vascular parameters			
WLR	0.373 ± 0.10	0.335 ± 0.98	0.106
Vessel diameter (μm)	109.4 ± 11.1	100.5 ± 14.4	0.002
Lumen diameter (μm)	79.9 ± 7.9	75.2 ± 8.5	0.009
Wall thickness (μm)	15.0 ± 4.2	12.7 ± 4.2	0.021
WCSA (μm)	4437.6 ± 1314.5	3615.9 ± 1567.8	0.014

Data are given as mean ± standard deviation.
CHF, congestive heart failure; dia, diastolic; RCF, retinal capillary flow; sys, systolic; WCSA, wall cross-sectional area; WLR, wall-to-lumen ratio.

Figure 1 Differences in retinal arteriolar parameters between subjects with CHF and controls.[39] CHF, congestive heart failure; LD, lumen diameter; VD, vessel diameter; WCSA, wall cross-sectional area; WT, wall thickness.



elevated BP by means of eutrophic arteriolar remodelling, which consists of rearrangement (and not growth) of smooth muscle cells. This leads to normalization of wall stress, accompanied by an increase in wall thickness but not necessarily WCSA.[1–4,15,20,27] Accordingly, Ritt *et al*. observed an increase in wall thickness in subjects with essential hypertension compared with normotensives without significant increase in WCSA.[2] On the long run, these alterations indicate maladaptive vascular processes and represent important indicators for end-organ damage in subjects with hypertension.[1,40,41] In subjects with severe, long-standing or secondary hypertension, a predominant growth response becomes evident, characterized by a greater wall thickness and WCSA going along with hypertrophia of smooth muscle cells.[4,27,42,43] Similar alterations could be observed in subjects with T2DM. An increased thickness of basal membranes and proliferation of extracellular matrix lead to an increase in both wall thickness and WCSA.[5,8,44] In the current study, an increase in both wall thickness and WCSA indicates a predominant growth response of retinal arterioles in subjects with CHF. The increase in both vessel and lumen diameter suggests a dilative component of structural alterations of retinal arterioles in subjects with CHF, as can be observed echocardiographically in subjects with CHF.

This finding might explain the lack of a significant difference in WLR between the two groups in the present study, with the ratio itself staying constant while both vessel and lumen diameter are increasing. In the literature, alterations in WLR have been described to be among the first manifestations of target organ damage for example in hypertension.[1,9,16–19] Ritt *et al*. described a higher WLR in hypertensive subjects compared with controls and a positive correlation between BP and WLR. BP was even found to be an independent determinant of WLR.[2,23] Vascular remodelling thereby leads to an increase in wall thickness and decrease in lumen diameter, resulting in a higher WLR.[1,2,27] In accordance to these findings, Rizzoni *et al*. observed a higher media-to-lumen ratio of subcutaneous small arteries and a higher WLR of retinal arterioles in hypertensive subjects compared with normotensives evaluated by SLDF.[21]

In the current study, we found no significant differences in RCF between subjects with CHF and controls, indicating neither hypoperfusion nor hyperperfusion in the retinal circulation. This finding suggests that baseline retinal

perfusion is maintained indicating a preserved physiological counter-regulation and autoregulation. In contrast, pulsed RCF was higher in the group of subjects with CHF. A widening of PP due to a mostly age-related increase in systolic and decrease in diastolic BP is known to be indicative of loss of arterial elasticity. Thereby, an increased PP and augmented pulsatile flow induce greater sheer stress on the endothelium of small arteries, which on the long run leads to endothelial dysfunction and microvascular damage.[45] Harazny *et al*. discovered a significantly exaggerated pulsed RCF (without any difference in mean RCF) in subjects with treatment-resistant hypertension compared with subjects with hypertension Stage 1 or 2 by means of SLDF, indicating vascular remodelling and microvascular damage in this group of subjects.[46]

Vascular structure and function play a key role in the pathophysiology of CHF.[47] Endothelial dysfunction and remodelling of the peripheral vascular system, for example the brachial artery, have been previously shown to be associated with the pathogenesis and progression of CHF.[48–51] Therefore, vascular remodelling represents a potential treatment target for new therapeutic options in patients with CHF.[29] Retinal microvascular structure and function parameters are known to reflect those in the systemic circulation,[40,41] and the role of retinal microcirculatory changes in subjects suffering from cardiovascular diseases has been described in large population-based studies.[10,14,52] During the last years, the role of microcirculatory alterations especially in subjects with CHF has gained growing attention.[11,53] By means of retinal vessel analysis, Nagele *et al*. recently demonstrated an impaired flicker light response of the retinal microvasculature in subjects with CHF suggesting a reduced vasodilatatory capacity.[54] Applying the same method, Barthelmes *et al*. showed that in subjects with coronary artery disease, retinal microvascular function is more impaired in the presence of CHF and reduced ejection fraction than in those without CHF.[55]

In this context, evaluation of retinal arteriolar abnormalities by means of SLDF represents an exceptional opportunity for assessment of the microcirculation non-invasively *in vivo* in patients with cardiac diseases. Microvascular structure and function are important surrogate parameters for macrovascular damage and may thereby represent interesting treatment targets for new CHF therapies.

Limitations

The current study has some limitations that need to be mentioned. First, in order to further characterize the above-mentioned dilatative component of retinal alterations, it would have been interesting to differentiate between subjects with different causes of CHF, such as ischemic or dilated cardiomyopathy or different entities, such as heart failure with reduced and mid-range ejection fraction. However, because of the small number of subjects in the current study, this differentiation would not show enough statistical power to draw valid conclusions. Second, the current study had an observational, cross-sectional design and included subjects with compensated CHF only. Therefore, the findings of the current study cannot be transferred to subjects with decompensated CHF or heart failure with preserved ejection fraction. Third, the group of subjects with CHF included subjects with cardiovascular risk factors such as hypertension and diabetes mellitus. However, both BP and glycaemic status were controlled in our study subjects, and BP was even higher in the control group than in the CHF group. For that reason, we did not exclude patients with hypertension from our analysis, and the influence of both factors on our results is regarded as rather low. Of note, there was a significant difference in gender distribution between the two groups due to consecutive enrolment of subjects. However, in the epidemiological study by Cífková *et al*., there were no differences in retinal vascular parameters between males and female participants[32] and, because the major determinant for retinal vascular parameters is age, that was the reason why matching for age was performed.

Conclusions

The current study analysed retinal parameters in subjects with CHF compared with controls by means of SLDF. We found hypertrophic remodelling of retinal arterioles in subjects with CHF indicative of similar changes in the systemic circulation.

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Conflict of interest

R.E.S. is a state employee of the Free State of Bavaria (University Hospital Erlangen)/Federal Republic of Germany. He is a member of the working group of 2013/2018 ESC/ESH guidelines for the management of arterial hypertension. R.E.S. received Speaker fees, Consultancy and Advisory Board fees from Bayer, Berlinchemie,

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