INTRODUCTION

The development of impaired skin microvascular function in hypertension is multifactorial, where increased vascular resistance, vascular rarefaction with reduced capillary network, impaired nitric oxide (NO)-dependent and NO-independent vasodilatory response, all are important factors for microvascular function. Impaired microvascular endothelial function with reduced NO availability evolves with increasing age. However, endothelial dysfunction induced by oxidative stress interfering with NO synthesis develops at an earlier stage in primary hypertension. In uncomplicated hypertension, vasoreactivity of the conduit arteries is mainly dependent on NO availability and endothelium-dependent vasodilation. In addition, skin microvascular function is regulated by metabolic factors such as glucose metabolism.
and insulin resistance, and impaired glucose uptake and increased peripheral resistance may in addition to endothelial dysfunction further deteriorate skin microvascular function.6,7

Skin microvascular dysfunction is present in individuals in the general population with cardiovascular (CV) risk factors and risk of developing type 2 diabetes6,9 and in patients with type 2 diabetes and the metabolic syndrome.10–12 Reduced endothelium-dependent vasodilatation of the skin is associated with coronary heart disease and future risk of CV events.13 In addition, heat-induced maximum reactive hyperemia may represent total microvascular reactivity of the skin, where impaired vasodilatation after local heating is associated with increased CV risk and risk of acute coronary syndrome, further enhanced in diabetic patients.13,14 Subendocardial viability ratio (SEVR) is a non-invasive estimate of myocardial oxygen supply and demand, calculated as the ratio of the area under the curve of the diastolic to systolic derived aortic pressure waveform.15,16 SEVR is associated with coronary flow reserve, and a reduced SEVR is associated with increased CV risk and worse prognosis in patients with diabetes and with chronic kidney disease.17–20

The metabolic syndrome and diabetes are associated with dyslipidemia and low levels of high-density lipoprotein cholesterol (HDL) levels, where impaired anti-oxidative capacity of HDL causes endothelial dysfunction and promotes inflammation and atherosclerosis.21,22 The anti-atherogenic effects of HDL are attenuated in type 2 diabetes, reducing endothelium-dependent vasodilatation.23 A disturbed glucose metabolism and impaired skin microvascular function is present in familial combined hyperlipidemia.24,25 Hypercholesterolemia seems to impair the vasoprotective functions of HDL by alterations of HDL expression in endothelial cells, as shown in animal studies.26 Thus, skin microvascular dysfunction is related to insulin resistance and dyslipidemia, where HDL seems to have an important role in regulating microvascular reactivity. Several biomarkers of metabolic status have been shown to serve as proxies of insulin resistance. An increased ratio of triglyceride/HDL (TG/HDL) is associated with insulin resistance and the metabolic syndrome, and future risk of ischemic heart disease in the general population.27–29 The triglyceride-glucose index (TyG), the product of fasting plasma glucose and triglycerides, is associated with insulin resistance and the metabolic syndrome, and future risk of developing diabetes.30,31 Furthermore, TyG is associated with subclinical atherosclerosis and an increased risk of CV events.32,33

Whether non-diabetic hypertensive patients have early changes in skin microvascular function due to early metabolic changes and dyslipidaemia with low HDL cholesterol has not been well studied. Thus, the present study aimed to evaluate skin microvascular vasoreactivity and coronary microvascular function in relation to lipid profile with signs of dyslipidemia and early development of insulin resistance in non-diabetic hypertensive patients.

2 | MATERIALS AND METHODS

The Doxazosin-ramipril study investigated women and men above 18 years of age with untreated mild-to-moderate primary hypertension (office systolic blood pressure 141–180 mm Hg and/or diastolic blood pressure 91–110 mm Hg). Exclusion criteria were ischemic heart disease, severe hypertension (180/110 mm Hg), chronic heart failure, arrhythmias, diabetes mellitus, and pregnancy. The primary aims of the study were to evaluate the effects of treatment with ramipril or doxazosin during 12 weeks on endothelial function and hemostasis, and the main results have been presented in detail elsewhere.34,35 We, here, report cross-sectional findings from vascular examinations and biochemistry regarding lipids and glucose control in untreated participants at baseline prior to randomization to active treatment. All vascular examinations were performed after overnight fasting and without intake of nicotine or caffeine, or any medications influencing endothelial function, in the supine position after 20 minutes of rest, at room temperature.34

This study is registered at ClinicalTrials.gov (NCT02901977) and at EudraCT (# 2007-000631-25), and was approved of by the appropriate Ethics committee. All subjects gave their oral and written consent to participate.

2.1 | Blood pressures measurements

Brachial blood pressure readings were obtained in the supine position by an oscillometric device (OMRON 705IT, OMRON Healthcare Co, Ltd. Kyoto Japan) on the dominant arm with an appropriately sized cuff, as a mean of three readings 1 min apart.

2.2 | Forearm skin microvascular function

Microvascular reactivity was assessed by laser LDF and transdermal iontophoretic drug administration and local heating (Periflux system 5000, PF 5010 LDPM Unit, PF5010 Temp Unit, and 481-1 Single Probe, Perimed, Järfälla, Sweden). First, basal cutaneous blood flow registration (in perfusion units, PU) was performed for 2–3 min. Second, local stimulation by a small electrical current (0.2 mA, for 60 s) was used for iontophoresis of ACh (Sigma-Aldrich AB, Stockholm, Sweden) and SNP (Hospira, Inc., Lake Forest, IL, USA), where a solution of 250 μl of ACh 1% or SNP was administered in small electrode chambers placed on the volar side of the forearm.3 A continuous registration was made for 15 min to detect maximum peak flux (in PU) for ACh and SNP, respectively. Third, LDF and local heating of forearm skin to +44°C for 6 min was used to evaluate the maximum cutaneous reactive hyperemia as a measure of total skin microvascular reactivity.34,36 Assessment of skin microvascular function by LDF and transdermal iontophoretic drug administration, and by LDF and local heating, are validated and reproducible methods.14,37,38 Microvascular function was also expressed as maximal cutaneous vascular conductance (CVC), calculated as cutaneous blood flow (in PU) divided by brachial mean arterial pressure (diastolic +1/3 (systolic – diastolic) blood pressure, in mm Hg) to account for blood pressure differences between patients.38
2.3 | Subendocardial viability ratio as a marker of coronary microvascular function

SEVR is a non-invasive estimate of myocardial oxygen supply and demand calculated as the ratio of (aortic diastolic pressure x time integral) to the (aortic systolic blood pressure x time integral), which is taken to represent the subendocardial perfusion capacity relative to myocardial contraction, that is, myocardial perfusion relative to cardiac workload.\textsuperscript{15-17} SEVR was derived from a general transfer function using pulse wave analysis (Sphygmocor, AtCor Pty Ltd, West Ryde, NSW, Australia) with applanation tonometry (Millar Instruments, Houston, TX, USA), as described elsewhere.\textsuperscript{17,39} Measurements were made prior to, and separate from, the evaluation of endothelium-dependent vasodilation of the resistance arteries with beta 2-adrenoceptor agonist stimulation (see below) to exclude confounding influence. SEVR has been validated with invasive coronary artery measurements in hypertensive patients without coronary heart disease and is associated with coronary flow reserve.\textsuperscript{17} However, SEVR may overestimate the diastolic pressure x time integral as it is derived from blood pressure measurements and not from left ventricular end diastolic pressure.\textsuperscript{40} SEVR is dependent of heart rate and the slope of diastolic decay, as well as to age and sex.\textsuperscript{17,18} This potential confounding was addressed by additional multivariable analyses.

2.4 | Endothelial function in resistance arteries and large arteries

To evaluate endothelium-dependent vasodilatation of the resistance arteries we used applanation tonometry and pulse wave analysis with additional beta 2-adrenoceptor agonist stimulation (terbutaline 0.25 mg sc; Bricanyl, AstraZeneca, Mölndal, Sweden).\textsuperscript{34,43} Recordings were performed before, and 15 and 20 min after the injection to evaluate the maximum effect of the beta 2-adrenoceptor agonist stimulation. The change in reflection index (RI), described as the relative change of height of the reflecting radial pulse waveform, was taken as a marker of endothelium-dependent vasodilatation of the resistance arteries.\textsuperscript{42} Thus, a smaller relative change in RI represents impaired endothelial function.

Endothelial function in conduit arteries was assessed in the non-dominant arm by flow-mediated vasodilatation (FMD) during post-ischemic hyperemia. Resting basal diameter of the brachial artery was measured for 1 min by a Vivid 7 Dimension ultrasound device with a 9 MHz linear transducer (GE Medical System, Horten, Norway). Thereafter, an inflated pneumatic tourniquet placed around the forearm to a pressure of 250 mm Hg for 5 min induced occlusion of the brachial artery. Post-ischemic reactive hyperemia was recorded after 30, 60, and 90 s to register the maximum diameter of the artery as a measure of FMD. Endothelium independent vasodilatation was induced after 10 min rest by 0.4 mg sublingual glyceryl trinitrate (GTN; Nitrolingual, G Pohl-Boskamp GmbH & Co KG, Hohenlockstedt, Germany). Relative changes in artery diameter were calculated from rest to 4 min following GTN administration.\textsuperscript{34} To calculate the endothelium-dependent in relation to endothelium independent vasodilatation, the endothelial functional index was calculated as the FMD/GTN ratio, as described elsewhere.\textsuperscript{34}

2.5 | Biochemical assessments

Routine biochemistry was analyzed by standard procedures from fasting blood samples obtained into appropriate Vacutainer tubes (Becton-Dickinson Co. Cedex, Meylan, France) on ice from an indwelling antecubital venous catheter after 20 min of supine rest. Low-density lipoprotein cholesterol (LDL) values were calculated by the Friedewald formula as total cholesterol – plasma HDL – (0.45 x fasting plasma TG).\textsuperscript{43} In this post hoc analysis, two indirect measures for estimation of metabolic status (i.e., insulin resistance) were used: the TyG-index, calculated as ln(fasting plasma glucose (mg/dl) x triglycerides (mg/dl)/2), and the TG/HDL ratio.\textsuperscript{30,44}

2.6 | Statistics

Data are presented as mean values ±SD, or medians and interquartile range, as appropriate. Skewed variables were logarithmically transformed. Associations were assessed by linear regression and Pearson’s correlation coefficients (r). Multivariable linear regression analyses between SEVR and lipid profile included HR, SBP, age, sex, and BMI, and for skin microcirculation, and macrovascular function

| TABLE 1 Baseline characteristics |
|---------------------------------|
| Male/female (n) | 45/26 |
| Age (years) | 54.5 ± 12.6 |
| Smokers (n) | 4 |
| BMI (kg/m\(^2\)) | 26.8 ± 4.7 |
| Office systolic BP (mm Hg) | 154 ± 10 |
| Office diastolic BP (mm Hg) | 93 ± 9 |
| Heart rate (beats/min) | 61 ± 8 |
| Plasma cholesterol (mmol/L) | 5.4 ± 1.1 |
| Plasma HDL (mmol/L) | 1.4 ± 0.4 |
| Plasma LDL (mmol/L) | 3.4 ± 0.9 |
| Plasma LDL/HDL | 2.66 ± 0.98 |
| Plasma triglycerides (mmol/L) | 0.96 [0.61–1.33] |
| TG/HDL | 0.65 [0.44–1.18] |
| Fasting plasma glucose (mmol/L) | 5.4 ± 0.6 |
| TyG | 6.74 ± 0.59 |
| Estimated GFR (mL/min/1.73m\(^2\)) | 90.4 ± 14.5 |
| UACR (mg/mmol) | 0.7 [0.4–1.1] |

Note: Data presented as mean values ±SD, or as median and interquartiles for 71 patients.

Abbreviations: BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TyG, triglyceride-glucose index; UACR, urine albumin-to-creatinine ratio.
included age, sex and BMI to account for potential confounding. All statistical tests were 2-sided and carried out to a significance level (p) of .05. The statistical program used was JMP version 15, SAS Institute Inc., Cary, NC, USA).

### RESULTS

#### 3.1 General

Baseline characteristics are presented in Table 1. About one-third of the study participants were women. Few were smokers. No patient was on statins or other lipid-lowering treatment, and fasting glucose values were in normal range. Values for indices of vascular function in various vascular beds are presented in Table 2.

#### 3.2 Microvascular reactivity in relation to lipid profile

ACh-mediated peak flux was related to HDL, but not to LDL, or the LDL/HDL ratio (Table 3; Figure 1A,B). Heat-induced maximum peak flux was related to HDL and to the LDL/HDL ratio, but not to LDL.
Table 3; Figure 1C,D). SNP-mediated peak flux and the ACh peak flux/SNP peak flux ratio did not relate to HDL, LDL, or the LDL/HDL ratio (Table 3). The results for the relative changes in peak flux after ACh, SNP and heat stimulation were similar (data not shown). CVC values for ACh-mediated peak flux and heat-induced peak flux showed similar results (Table 3). Multivariable analysis confirmed that microvascular reactivity was independently related to HDL, for endothelium-dependent peak flux ($p = .011$) and heat-induced maximum peak flux ($p = .017$), respectively. In contrast to skin microcirculation, indices of coronary artery microvascular function assessed by SEVR were inversely related to LDL, but was unrelated to HDL, and the LDL/HDL ratio (Table 3; Figure 2A,B). However, this relation to LDL was not retained in a multivariable analysis ($p = .24$).

3.3 | Macrovascular endothelial function in relation to lipid profile

Endothelium-dependent vasodilation in conduit arteries (as assessed by FMD) tended to relate to HDL, but not to LDL, or the LDL/HDL ratio (Table 3). Endothelium independent vasodilation (as assessed by GTN) did not relate to HDL, LDL, or the LDL/HDL ratio (Table 3). However, the endothelial functional index (i.e., FMD/GTN) was related to HDL but not to LDL, or the LDL/HDL ratio (Table 3; Figure 3A,B). Endothelial function in resistance arteries (as evaluated by the RI change) related inversely to HDL, and related to the LDL/HDL ratio, but not to LDL, that is, a smaller reduction in RI change after beta 2-agonist stimulation was related to dyslipidemia with low HDL (Table 3; Figure 3C,D). Multivariable analysis confirmed an independent relation between RI and HDL ($p = .017$) but not to Endothelial functional index and HDL ($p = .15$).

3.4 | Microvascular reactivity and endothelial function in relation to markers of metabolic status

Peak flux to ACh was inversely related to the TG/HDL ratio and tended to inversely relate to TyG (Table 4; Figure 4A,B). SNP-induced peak flux, the ACh peak flux/SNP peak flux ratio, and heat-induced maximum peak flux were unrelated to TyG and TG/
HDL ratio (Table 4; Figure 4C,D). Corresponding CVC values for skin microvascular function showed similar results (Table 4). In contrast, coronary microvascular function assessed by SEVR did not relate to TyG or the TG/HDL ratio (Table 4) and large artery function (FMD, GTN, endothelial function index and RI change) was unrelated to measurements of insulin resistance (data not shown).

### DISCUSSION

This appears to be the first study in non-diabetic hypertensive patients to explore endothelial function in different vascular beds in relation to signs of dyslipidemia and insulin resistance. Our main findings are, first, that impaired skin microvascular function related with signs of dyslipidemia with lower HDL cholesterol levels, and with insulin resistance. Second, heat-induced maximum reactive hyperemia, appears to be a robust method to evaluate total skin microvascular function in non-diabetic primary hypertension. Third, skin microvascular function and SEVR, as a marker of coronary microvascular function, showed different associations to lipid profile.

Our results showed that reduced ACh-mediated peak flux was associated with low HDL, and RI was inversely related to HDL. These findings confirm the interrelation between HDL and the endothelium with a vasoprotective role of HDL. Of note, the function of the HDL is important for the NO pathway, oxidative capacity, vascular inflammation, and for endothelial function. Thus, our results suggest that hypertensive patients with dyslipidemia and low HDL levels have early signs of skin microvascular dysfunction and impaired endothelium-dependent vasodilation. In addition, maximum peak flux after local heating was related to HDL and the LDL/HDL ratio. This relation was maintained also when CVC was calculated to account for differences in mean arterial pressure. Thus, as for ACh-mediated vasodilation, impaired heat-induced maximum reactive hyperemia was associated with low HDL ratio (Table 4; Figure 4C,D). Corresponding CVC values for skin microvascular function showed similar results (Table 4). In contrast, coronary microvascular function assessed by SEVR did not relate to TyG or the TG/HDL ratio (Table 4) and large artery function (FMD, GTN, endothelial function index and RI change) was unrelated to measurements of insulin resistance (data not shown).
HDL. In hypertension, skin blood flow is impaired due to a reduced endothelium-dependent vasodilatation, and to a diminished neurogenic response after local heating. Heat-induced maximum reactive hyperemia is induced by an early direct axon mediated reflex, and by a delayed response mediated mainly through NO. Thus, evaluation of global microvascular function by heat-induced maximum reactive hyperemia provides information about total skin microvascular reactivity. Furthermore, our data support the contention that heat-induced maximum reactive hyperemia is reduced in primary hypertension and relates to an early stage of dyslipidemia with low HDL.

We used the TG/HDL ratio and TyG as markers of insulin resistance. Our results showed that an impaired response to ACh-mediated vasodilatation related inversely to the TG/HDL ratio. In contrast, maximum reactive hyperemia by local heating did not relate to the TG/HDL ratio. There was a weaker relation with TyG and functional measures of skin microcirculation, compared to the TG/HDL ratio. However, our study subjects had no signs of diabetes, with fasting glucose in normal range and no overt metabolic syndrome, which may explain this difference. Endothelial function in the conduit or resistance arteries (as assessed by FMD and the RI change) did not relate to metabolic markers. Thus, glucose metabolic status may be less important for conduit and smaller resistance artery function, as compared to skin microvascular function where glucose metabolism directly influences vasoreactivity.

SEVR was not related to HDL or markers of insulin resistance, in contrast to skin microvascular function. Although SEVR has been shown to associate with invasively measured coronary flow reserve in hypertensive subjects with no established coronary artery disease, several potential confounders may limit its use as a marker of coronary microvascular function. Furthermore, reduced SEVR is associated with increased CV risk and worse prognosis in patients with diabetes and chronic kidney disease. In addition, lower SEVR is associated with development of microalbuminuria in type 1 diabetes, and in chronic kidney disease, and with the severity of peripheral arterial disease with reduction of ankle brachial index. Thus, a reduced SEVR is associated with endothelial dysfunction and atherosclerosis. Endothelial heterogeneity with differences in vascular structure and function may explain the poor interrelationship between microvascular function in the skin, myocardium, and other organs. Thus, impaired skin microvascular function and reduced coronary microvascular capacity observed in this study may demonstrate different aspects of CV risk.

There are several strengths to this study. We investigated different vascular beds with established methods representing microvascular and macrovascular function. Data on reproducibility have been presented. However, there are limitations to consider. The study population was relatively small, which raises a risk for type 2 errors, and there was no healthy control group for comparison. Evaluation of skin microvascular function is subject to confounding by external influence, including changes in heart rate, blood pressure, skin temperature, and vascular sympathetic tone. However, the experimental conditions were strictly standardized with vascular examinations performed on one single occasion. In addition, we used CVC as internal validation for skin microvascular measurements to account for differences in baseline mean arterial pressure among patients, with similar results. We did not evaluate myocardial microvascular function invasively. However, indirect assessment of microvascular function by SEVR has been validated to invasive measurements of myocardial microcirculation and to cardiovascular outcome, as discussed above. We used the TG/HDL ratio and

![Figure 4](image-url)
TyG as indirect markers of metabolic status in this post hoc analysis. Unfortunately, no direct measurements of insulin sensitivity or stored samples are available.

5 | PERSPECTIVES

Our results in patients with uncomplicated non-diabetic hypertension suggest early signs of microvascular dysfunction associated to dyslipidemia with low HDL and insulin resistance. This is in consort with observations in type 2 diabetes and in the metabolic syndrome.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

AJ designed the study, interpreted data, and wrote manuscript. MK interpreted data and gave expert comments on the manuscript. TK conceptualized the study, interpreted data, and edited the manuscript.

DATA AVAILABILITY STATEMENT

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

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