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RESEARCH ARTICLE | *Integrative Cardiovascular Physiology and Pathophysiology*

Tissue optical perfusion pressure: a simplified, more reliable, and faster assessment of pedal microcirculation in peripheral artery disease

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Horstick G, Messner L, Grundmann A, Yalcin S, Weisser G, Espinola-Klein C. Tissue optical perfusion pressure: a simplified, more reliable, and faster assessment of pedal microcirculation in peripheral artery disease. *Am J Physiol Heart Circ Physiol* 319: H1208–H1220, 2020. First published September 18, 2020; doi:10.1152/ajpheart.00339.2020.—Oscillometry is an alternative to continuous-wave Doppler (cw-Doppler) to determine peripheral artery disease (PAD) severity using the ankle-brachial index (ABI). cw-Doppler ABI differentiates systolic pressure of ATP and ADP where either one of both values in most patients is higher (high) and the other value is lower (low). In contrast, oscillometric ABI measures the strongest signal and hence misses the lower value. Both do not take pedal perfusion into consideration. Simultaneous determination of tissue microperfusion cares for pedal PAD. ABI was determined by cw-Doppler and oscillometry. Tissue optical perfusion pressure (TOPP) was taken from the first toe using photoplethysmography. 323 patients were evaluated retrospectively in 3 independent groups. *group 1* (99 patients) compared TOPP and oscillometric ABI with systolic cw-Doppler-pressure and cw-Doppler ABI. In *group 2* (103 patients) TOPP was compared with toe pressure (TP). In *group 3* (121 symptomatic patients) TOPP and ABI at rest and after stress were compared (ultrasound examination and magnetic resonance angiography (MRA) or computer tomography angiography (CTA) as control). Bland-Altman-plot analysis presented no significant difference between oscillometric ABI and the high cw-Doppler ABI (*group 1*). TOPP showed a difference of 26mmHg to the low cw-Doppler-pressure and none to the high cw-Doppler-pressure. In *group 2* TOPP correlates to TP but presented a difference of 37 mmHg. *group 3* showed weak or no correlation between ABI and walking distance. Oscillometric ABI correlates significantly to TOPP. To conclude, data after stress present a better correlation than at rest. We conclude that TOPP provides absolute values of pedal macro-/microcirculation at rest and after stress tests.

NEW & NOTEWORTHY This new application of photoplethysmography investigated the microcirculation in peripheral artery disease at the level of the toe pad and determined the tissue optical perfusion pressure as the first pulsatile signal during automatic cuff deflation at the ankle. It is the first time that this method has been integrated for simultaneous routine examination in an automatic oscillometric ankle-brachial index (ABI) system. This quick and simple measurement technique provides clinical information on the microcirculation downstream the routine ABI measurement at rest and in particular after stress test.

cw-Doppler ABI; oscillometric ABI; pedal microperfusion; peripheral artery disease; tissue optical perfusion pressure

INTRODUCTION

Approximately 200 million people are affected by peripheral artery disease (PAD) of the lower extremities worldwide. PAD appears usually after the age of 50 yr, and by the age of 80 yr every fifth person has a form of PAD. The prevalence of PAD in two West European countries between 60 and 90 yr of age is between 10 and 20% and even higher in diabetic patients. One-fifth to one-third of them are symptomatic. The cardiovascular mortality of asymptomatic patients is almost the same as for symptomatic PAD. Measurement of ankle-brachial index (ABI) at rest is an independent risk factor of cardiovascular mortality in symptomatic and asymptomatic PAD as well as pulse wave velocity (18, 39). However, early-stage PAD might be missed because current measurement methods are not accurate enough, since they focus on flow limitation at rest. Measurements after stress testing using the reference method of continuous wave (cw)-Doppler might be time consuming and might have issues of human error.

ABI can be measured conventionally by cw-Doppler or alternatively by oscillometry. Oscillometric ABI usually uses pulse wave analysis, which can be hindered by technical aspects. Both methods do not consider pedal perfusion. However, critical limb ischemia with consecutive foot ulcers and minor amputations are below the measuring thresholds of ABI. Since peripheral interventions enter the region of the pedal arteries, additional criteria determining the improvement of macrocirculatory and microcirculatory hemodynamics are of utmost interest. According to the Trans-Atlantic Inter-Society Consensus (TASC), one of the parameters for evaluation of critical limb ischemia (CLI) is an absolute toe pressure (TP) of less than 30–50 mmHg (23). Rutherford and co-authors define severe claudication in CLI if ankle pressure drops below 50 mmHg after exercise testing. This idea is supported by data of skin perfusion pressure in healing and nonhealing ulcers (15, 41, 45, 46). The technical acquisition of TP is still a matter of concern, mostly noted in low-pressure situations. The idea that TP measurements may replace ankle pressure measurements for screening of chronic CLI has not yet been clarified (30). A low correlation of TP and ankle pressure has been reported (30).

The standard reference technique uses handheld cw-Doppler to measure systolic ankle pressure, taking the first signal of the target vessel during ankle pressure cuff deflation. In contrast, automatic oscillometry detects the strongest pulse wave signal, reflecting the mean arterial pressure. In this context, the pressure transducer system's technical sensitivity is very important (6,

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25, 29, 32, 38, 44, 47, 49). Using an infrared photoplethysmography (PPG) sensor for the determination of the systolic pressure at the fingertips and toe tips to measure ABI was reported to provide a good correlation to cw-Doppler ABI (19, 42). Bilateral measurement of the infrared signal has been published (4). However, the published measurements were performed sequentially, thereby allowing for a hyperemic stimulation due to repeated occlusive pressure measurements. Therefore, an all-in-one solution would be preferable.

Automatic oscillometric analysis of the pulse wave with ECG registration and measurement of the tissue perfusion pressure by optical PPG can provide such a one-stop-shop analysis (3, 14). Placement of a PPG sensor at the tip of the toe, as presented in this study, to obtain the first pulsatile signal of tissue microcirculation [tissue optical perfusion pressure (TOPP)] during ankle cuff deflation could provide further information on peripheral microperfusion at rest and immediately after exercise.

MATERIALS AND METHODS

Study Design

We examined retrospectively the data of 323 patients in three independent groups who were admitted to an outpatient office (Cardiovascular Center Neustadt Weinstrasse) with suspected PAD (Table 1). The oscillometric system used for examination (Angio Experience Pro 8; Sonotechnik, Maria Rain, Austria) had not been validated previously. Therefore, 99 patients in *group 1* were analyzed to examine the correlation of oscillometry to the reference method of cw-Doppler and to the new method of TOPP. Since the determination of toe pressure (TP) is the measurement of choice for PAD in diabetic patients with media sclerosis of the lower leg arteries, the correlation of TP to TOPP in *group 2* (n = 103 patients) was examined; 83 patients thereof had the circumference of the ankle and the first toe measured to determine the ankle and toe circumference cuff width ratio.

For the first proof of concept in *group 3*, 121 symptomatic patients with documented PAD by ultrasound and magnetic resonance angiography (MRA) or computed tomography angiography (CTA) were examined at rest and after stress by simultaneous TOPP and oscillometric ABI measurement. Patients' characteristics of all groups are listed in Table 1. According to the Fontaine and Rutherford classifications, the level of disease tended to be higher in *group 3* with symptomatic and definitely proven PAD in contrast to *groups 1* and *2* with suspected PAD. *Groups 1* and *2* included a number of patients with suspected PAD who turned out to have PAD without significant flow limitations.

For measurement of the oscillometric ABI and TOPP, an eight-channel oscillometry device was used (Angio Experience Pro 8; Sonotechnik, Maria Rain, Austria) with the simultaneous registration of two PPG channels (Angio Experience Phlebo; Sonotechnik, Maria Rain, Austria; Fig. 1). In addition to oscillometry, the system also provides the conventional measurement of ABI using the reference standard of cw-Doppler (8 MHz, HiDopp 300; MTB Switzerland). TP determination was performed separately with toe pressure cuff occlusion and registration of the PPG signal (Angio Experience Phlebo) at the tip of the first toe while deflating the toe pressure cuff. TOPP at the first toe was documented simultaneously in 10 mmHg increments during automatic ankle pressure cuff deflation. All patients of *group 3* with rest and stress examinations had received an extensive ultrasound examination including determination of ankle peak systolic velocity (APSV) and MRA or CTA.

In 20 healthy subjects, the appearance of the TOPP signal at the first toe and at the dorsal pedal artery (ADP) was documented during ankle pressure cuff deflation. Simultaneous PPG signal detection at the pad of

Table 1. *Clinical characteristics, comorbidities, and PAD classification from patient history*

	Group 1: cw-Dopp- vs. Osci ABI	*Group 2*: TOPP vs. TP	*Group 3*: symp. PAD
n	99	103	121
Age, yr	73 ± 10.6	72.1 ± 10.1	70.6 ± 9.5
Female sex, *n* (%)	39 (39.4)	40 (38.8)	43 (35.5%)
Mean height, cm	169.6 ± 9	170.5 ± 8.5	170.3 ± 8.3
Weight, kg	78.5 ± 17.6	78.1 ± 16	78.1 ± 14.6
Body mass index, kg/m^2	27.1 ± 4.8	26.8 ± 4.5	26.9 ± 4.4
CVD, *n* (%)	32 (32.3)	27 (26.2)	77 (57.9)
CVD with TIA or stroke, *n* (%)	8 (8.1)	11 (10.7)	16 (12)
CAD, *n* (%)	24 (24.2)	22 (21.4)	32 (24)
Arterial hypertension, *n* (%)	84 (84.8)	82 (79.6)	108 (81.2)
Current smoking, *n* (%)	30 (30.3)	43 (41.7)	64 (48.1)
Hypercholesterinemia, *n* (%)	45 (45.5)	47 (45.6)	64 (48.1)
Diabetes, *n* (%)	29 (29.3)	28 (27.2)	42 (31.6)
Renal insufficiency, *n* (%)	2 (2)	5 (4.9)	2 (1.5)
Orthopedic diseases, *n* (%)	30 (30.3)	23 (22.3)	41 (30.8)
Fontaine classification, *n* (%)			
F I	46 (46.5)	58 (56.3)	15 (12.4)
F IIa	36 (36.4)	26 (25.2)	65 (53.7)
F IIb	16 (16.2)	19 (18.4)	41 (33.9)
F III	1 (2.0)	0 (0)	0 (0)
F IV	0 (0)	0 (0)	0 (0)
Rutherford classification, *n* (%)			
R 0	44 (44.4)	58 (56.3)	6 (5)
R 1	42 (42.4)	27 (26.2)	7 (5.8)
R 2	7 (7.1)	15 (14.6)	45 (37.2)
R 3	5 (5.1)	3 (2.9)	63 (52.1)
R 4	1 (2.0)	0 (0)	0 (0)
R 5	0 (0)	0 (0)	0 (0)
R 6	0 (0)	0 (0)	0 (0)

Values are means + SD and percentages; *n*, number of patients; (%), percentage of all patients; cw-Dopp., continuous wave-Doppler; PAD, peripheral artery disease; Osci-ABI, oscillometric ankle-brachial index; TP, toe pressure; TOPP, tissue optical perfusion pressure; CVD, cerebrovascular disease; CAD, coronary artery disease; TIA, transient ischemic attack.

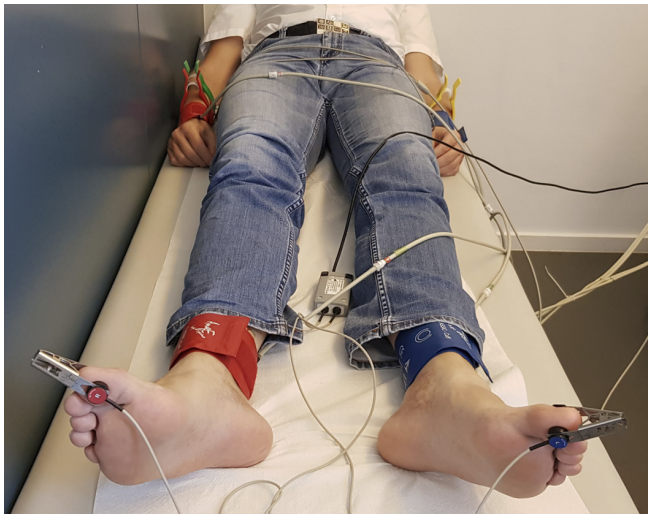


Fig. 1. Photoplethysmographic (PPG) sensors on the large toe at the foot for determination of tissue optical perfusion pressure (TOPP) and pressure cuffs at the ankle on the right (red) and left (blue) lower limb.

the first toe and the ADP always generated pulsatile signals at the same pressure level (Fig. 2). This was a control group for the assessment of the TOPP method.

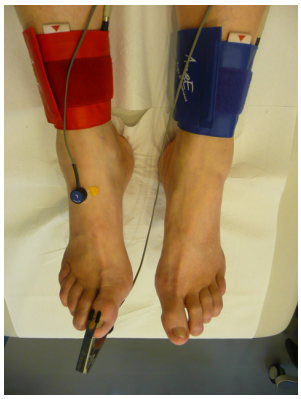
Starting with a software version including TOPP in the outpatient office in 2015, we used oscillometry and cw-Doppler simultaneously in the patients' examinations. The order in which measurement techniques took place was changed to avoid a bias due to the order of the examination procedures. The state's ethics committee of Rhineland-Palatinate (Rheinland-Pfalz) approved the protocol of retrospective data analysis. Informed consent was not required.

Methods

Systolic pressure was achieved with a biphasic handheld cw-Doppler probe at the target vessels (ADP, arteria dorsalis pedis) and posterior tibial artery (ATP, arteria tibialis posterior)) at the ankle by deflating the proximal ankle pressure cuff. The higher value of the ATP and ADP was named "high" and the other "low." At the brachial artery, a standard upper arm cuff was used, and at the wrist and ankle a pressure cuff with a cuff width of 10 cm was used. At each target artery (ADP, ATP) the cw-Doppler signal was registered acoustically and visually on screen during automatic pressure cuff deflation. Two skilled operators with experience of more than 5,000 (S. Yalcin) and 10,000 (A. Grundmann) examinations performed the measurements.

The cuff width at the toe for TP measurement was 2 cm. In 83 patients of *group 2*, the circumferences of the ankle and the first toe were measured to determine the circumference/cuff width ratio at the ankle and the first toe. The deflation of both toe cuffs was performed automatically.

Determination of the oscillometric ABI in *groups 1* and *2* was performed using automatic pressure deflation of all four pressure cuffs (wrist, ankle) from 200 to 20 mmHg. Documentation of the original pulsatile signals on screen was recorded at 10-mmHg steps, while the calculations for oscillometric ABI were performed by software calculation from the original signals. The largest amplitude, reflecting mean arterial pressure, was used to determine oscillometric ABI (34). The



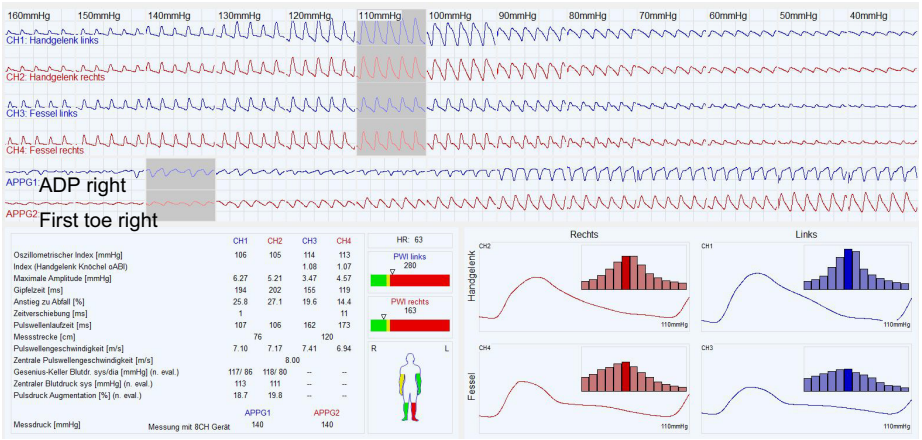


Fig. 2. Photoplethysmographic (PPG) sensors on the large toe (red) at the right foot and the dorsal pedal artery (ADP, blue) for simultaneous determination of tissue optical perfusion pressure (TOPP) and the ADP signal during pressure cuff deflation. The examinations in healthy subjects revealed a simultaneous signal appearance during ankle pressure decrease at both sensors, as shown in the present example (140 mmHg).

simultaneously acquired infrared PPG signal represented the tissue perfusion at the very end of the first toe's microcirculation and was established as the TOPP of the toe (Fig. 1). Beside the PPG sensor a sensor for determination of the temperature on the skin surface was integrated. Examinations at rest were performed after a rest period of 10 min in supine position.

In *group 3*, we used an oscillometric program with automatic pressure deflation from 160 to 40 mmHg. Documentation of the original pulsatile signal was recorded using the same procedure as described above. Absence of a pulsatile PPG signal below the threshold of 40 mmHg were documented as 30 mmHg.

The hemodynamic examinations in *group 3* were performed at rest and directly after defined treadmill exercises. Exercises consisted of a constant-load protocol (12%, 3.2 km/h) measuring initial claudication distance (ICD; pain-free walking distance) and absolute claudication distance (ACD; absolute walking distance, maximum 300 m) (31).

The ultrasound examination included determination of the abdominal aorta's Doppler spectrum, both common iliac and external iliac

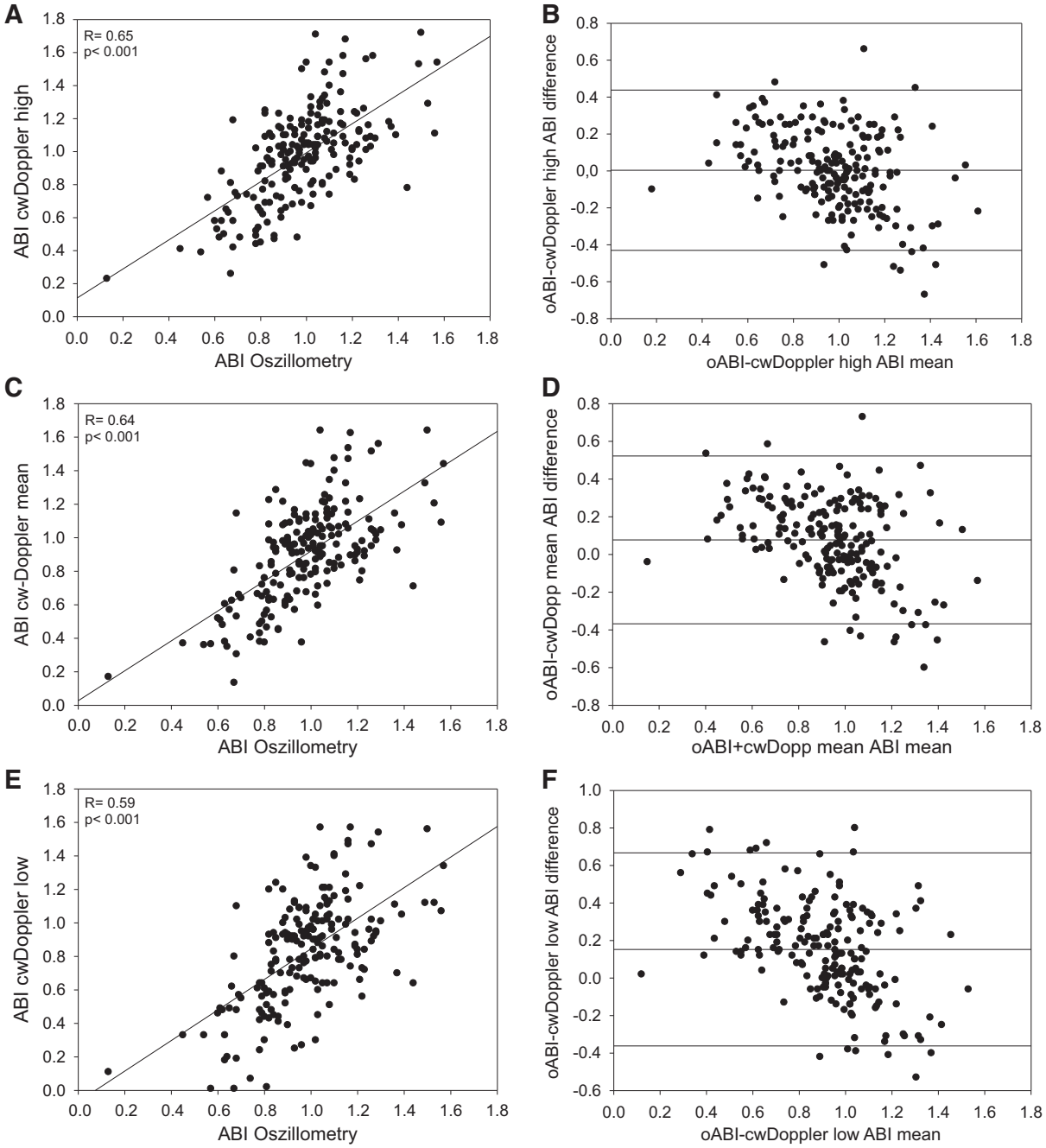


Fig. 3. Regression analysis of continuous wave-Doppler (cw-Doppler) ankle-brachial-index (ABI) vs. oscillometric ABI (oABI) and corresponding Bland–Altman plot analysis. *A* and *B*: high cw-Doppler ABI vs. oABI (*A*) and Bland–Altman plot (*B*). *C* and *D*: mean cw-Doppler ABI vs. oABI (*C*) and Bland-Altman plot (*D*). *E* and *F*: low cw-Doppler ABI vs. oscillometric ABI (*E*) and Bland–Altman plot (*F*). Solid lines in graphs *B*, *D*, and *F* represent means ± 2× SD. Data present an overestimation of oABI in contrast to mean and low cw-Doppler ABI. There is almost no difference between oABI and high cw-Doppler ABI (*group 1*, *n* = 99: 39 female, 60 male).

arteries. At the level of the upper leg, we examined the velocities of the common femoral, proximal, and medial superficial femoral artery and the profunda femoral artery and popliteal artery. At the lower leg, the distal anterior artery (ATA), the posterior tibial artery, and the distal peroneal artery were examined as well as the ADP and the ATP at the ankle. Compared with previous publications, we calculated the ankle peak systolic velocity from the Doppler of the ATP and distal ATA (APSV-ATA). Correlation of APSV-ATA to the severity of PAD and Rutherford classification grades 0, 1, and 2 or higher have been published (8, 9). Additionally, we tested another calculation for APSV by using the velocities of the ADP and ATP (APSV-ADP).

Statistical Analysis

Statistical analysis was performed with Sigma Stat 3.1. (Jandel Corp., San Jose, CA).

The statistical significance of differences between two groups (TOPP vs. TP, circumference ratio ankle vs. toe) were determined by unpaired two-sided Student's *t* test. Data between groups in the article are presented as means ± SE.

Differences between three and more groups were statistically analyzed with one-way ANOVA comparing several groups. If values did not show a normal distribution, ANOVA for nonparametric values (Kruskal–Wallis test) with the multiple comparison method (Dunn's method) was applied. Statistical significance was accepted at an error probability of $P < 0.05$ after pairwise testing.

To determine the correlation between two sets of values, a univariate linear regression method was used. A P value < 0.05 was considered statistically significant. Bland–Altman plots were used to compare the novel method to the reference method (e.g., oscillometry s. vs. cw-Doppler). Solid lines in the plots represent means ± SD2 (10).

RESULTS

Results of Group 1

Correlation of oscillometric ABI vs. cw-Doppler ABI. The results of cw-Doppler ABI in *group 1* of the ADP and ATP were grouped in high and low systolic pressure and compared with oscillometric ABI for each extremity. Additionally, the mean ABI from ADP and ATP was calculated. There was a significant correlation between oscillometric ABI and high cw-Doppler ABI as well as mean and low cw-Doppler ABI. The best correlation was found for oscillometric ABI vs. high cw-Doppler ABI ($r = 0.65$, $P < 0.001$), indicating almost no difference in the Bland–Altman plot (ABI difference 0.0038 ± 0.0155). The regression analysis for mean and low cw-

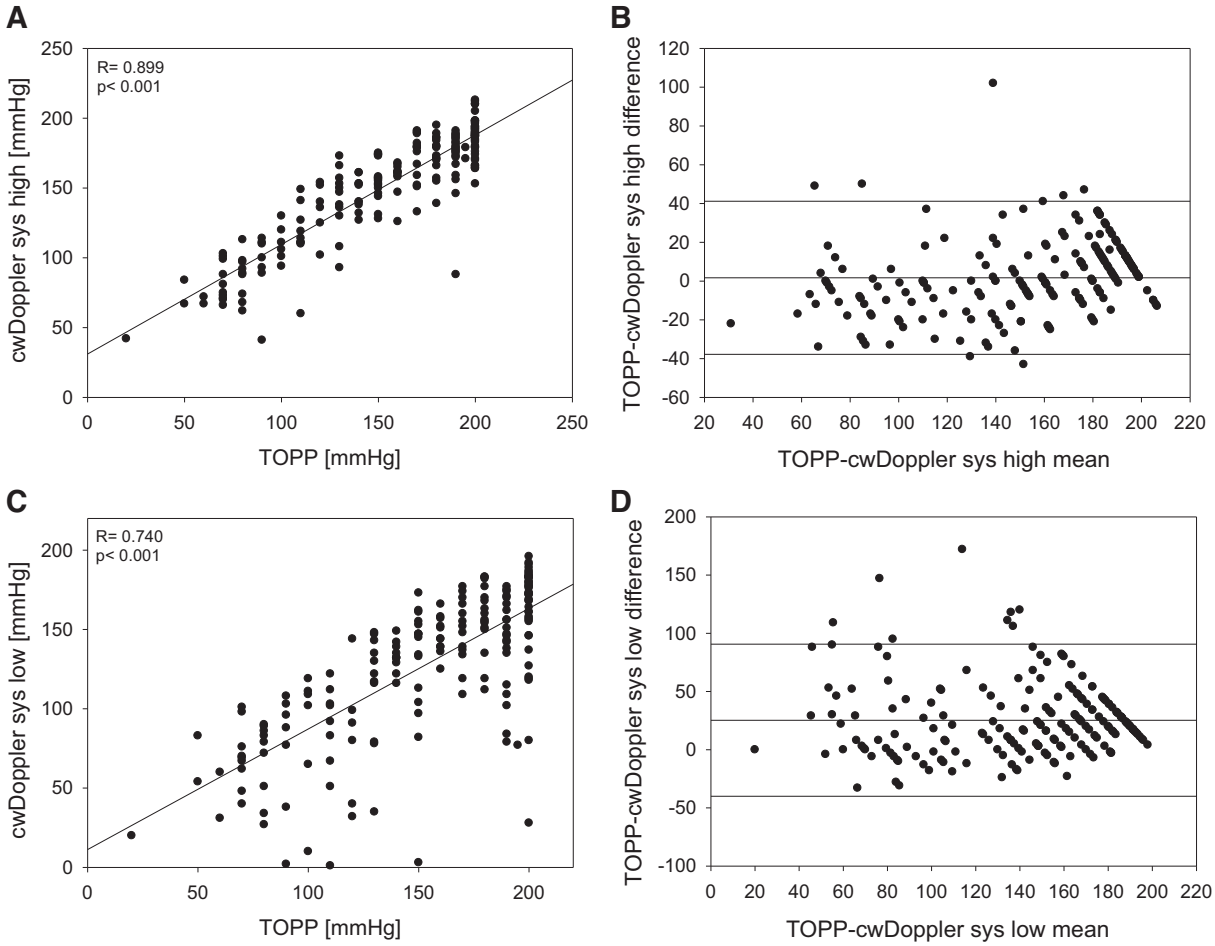


Fig. 4. Regression analysis of tissue optical perfusion pressure (TOPP) vs. high systolic continuous-wave-Doppler (cw-Doppler) pressure and vs. low systolic cw-Doppler-pressure. *A* and *B*: high cw-Doppler pressure vs. TOPP (*A*) and Bland–Altman plot (*B*). *C* and *D*: low cw-Doppler pressure vs. TOPP (*C*) and Bland–Altman plot (*D*). Solid lines in graphs *B* and *D* represent means ± 2×SD. Data present an overestimation of the TOPP vs. low systolic cw-Doppler pressure but almost none between TOPP and high systolic cw-Doppler pressure (*group 1*, $n = 99$: 39 female, 60 male).

Doppler ABI was significant (mean: $r = 0.64$, $P < 0.001$, low: $r = 0.59$, $P < 0.001$). The Bland–Altman analysis resulted in a difference for oscillometric ABI vs. mean and low cw-Doppler ABI (mean cw-Doppler ABI: 0.077 ± 0.016 and low cw-Doppler ABI: 0.15 ± 0.018; Fig. 3).

Pairwise testing presented a significant difference for high cw-Doppler ABI vs. low ($P < 0.001$) and vs. mean ($P < 0.001$). The oscillometric ABI was significantly higher vs. low ($P < 0.001$) and vs. mean cw-Doppler ABI ($P < 0.001$). No significant difference was seen between high cw-Doppler ABI and the oscillometric ABI ($P > 0.05$) and between mean vs. low cw-Doppler ABI ($P < 0.05$). The oscillometric system used in this setup presented a statistically significant correlation to the reference method of cw-Doppler.

Correlation of TOPP vs. systolic cw-Doppler-pressure. The analysis of TOPP and systolic cw-Doppler-pressure in *group 1* presented a significant correlation between TOPP and high systolic cw-Doppler-pressure ($r = 0.899$, $P < 0.001$) with almost no difference in the Bland–Altman analysis (1.69 ± 1.41 mmHg). The correlation between TOPP and low cw-Doppler-pressure was significant ($r = 0.74$, $P < 0.001$); however, there was a distinct difference in the Bland–Altman analysis (25.3 ± 2.34 mmHg; Fig. 4, *A–D*). Pairwise testing between TOPP, high, and low cw-Doppler pressure presented a significant difference of low cw-Doppler-pressure to TOPP and high cw-Doppler-pressure [TOPP 152.3 ± 3.2 mmHg, cw-Doppler high 150.5 ± 2.8 mmHg, cw-Doppler low 127.0 ± 3.3 mmHg; 95% confidence interval (CI): 146, 158.6 vs. 145, 156 vs. 120.5, 133.5; Fig. 5]. Between TOPP and high cw-Doppler systolic pressure there was no significant difference and an excellent r value of the correlation.

Results of Group 2

Correlation of TOPP vs. TP. The regression analysis of TOPP and TP in *group 2* showed a significant result ($r = 0.77$, $P < 0.001$; Fig. 6*A*). In contrast, there was a clear difference of TOPP and TP in the Bland–Altman analysis (37.0 ± 1.88 mmHg; Fig. 6*B*). TOPP is significantly higher than TP (TOPP 121.8 ± 2.8 mmHg, TP 84.8 ± 2.7 mmHg, 95% CI: 116.2, 127.4 vs. 79.4, 90.2, $P < 0.001$; Fig. 6*C*).

Circumference to pressure cuff width ratio of the ankle vs. first toe. In *group 2*, circumference-to-pressure cuff width ratio of the ankle and the first toe was calculated in 83 patients. The mean ratio of the circumference /pressure cuff ratio at the ankle was significantly lower than at the first toe (2.1 ± 0.02 vs. 3.39 ± 0.06, $P < 0.001$, 95% CI: 2.06, 2.14 vs. 3.27, 3.51). Since the anatomy of the larger ankle with a broad cuff is different from that of the smaller toe, one assumption is that the cuff at the toe might present a higher constriction on the smaller arteries and therefore lower TPs.

Results of Group 3: Results of Symptomatic PAD Patients at Rest and after Stress

Clinical characteristics and comorbidities of the patients. In *group 3*, the mean age was 70.6 ± 9.5 yr; 78 patients (64.5%) were male and 43 patients were female (35.5%). The BMI of the complete cohort was 26.9 ± 4.4 kg/m^2.

Additionally, cerebrovascular disease (CVD) was found in 58% of the patients, and 12% had a former history of *transient ischemic attack* or stroke. Coronary artery disease (CAD) coexisted in 24%. When we consider further cardiovascular risk factors (CVRF), 81% had hypertension, 48% smoked, 48% suffered from hypercholesterinemia, and 32% suffered from diabetes. Renal disease was found in 1.5% of the patients (Table 1), and 31% of the patients suffered from orthopedic disorders of the lower spine, hip, knee, or feet, thereby adversely affecting the differentiation of real claudication with regard to the pain-free walking distance (ICD).

The examination of the claudication distance revealed 34 patients (28%) who performed the complete distance of 300 m (ACD). During the test, 18 patients did not complain of claudication, in contrast to their history of claudication under daily circumstances. The majority of the patients complained of claudication after less than one-half of the maximum distance of 300 m ($\leq$150 meters, $n = 88$) and stopped exercise soon after (ICD vs. ACD, $r = 0.77$). The mean ICD was 126 ± 8.1 m and mean ACD 179 ± 8.4 m (95% CI: 110, 142 vs. 162, 196).

Correlation of ABI vs. ICD and ACD. The difference of the ABI was statistically significantly higher at rest than after stress testing (0.84 ± 0.01 vs. 0.57 ± 0.02, 95% CI: 0.82, 0.86 vs. 0.54, 0.60, $P < 0.001$). With regard to the correlation of ABI to ICD, there was only a weak correlation at rest ($r = 0.27$, $P = 0.003$). After stress testing, the correlation was almost the same ($r = 0.25$, $P < 0.006$). Additionally, the correlation of ACD to ABI at rest was low ($r = 0.28$, $P = 0.002$), and after stress testing no significant correlation was observed ($r = 0.01$, $P = 0.28$). The claudication distance can be an inadequate predictor of the measured ABI at rest and after stress for some subjects.

Correlation of TOPP vs. ICD and ACD. The TOPP was statistically significantly higher at rest than after stress testing (107 ± 2.5 vs. 68 ± 2.8mmHg, 95% CI: 102, 112 vs. 62.5, 73.5, $P < 0.001$). The correlation of TOPP to the ICD before and after stress testing was not significant (TOPP at rest vs. ICD: $r = 0.15$, $P = 0.098$; TOPP after stress vs. ICD: $r = 0.15$, $P = 0.094$). No correlation was seen for the data of ACD to TOPP before and after stress. (TOPP at rest vs. ACD: $r = 0.16$, $P = 0.086$; TOPP after stress vs. ACD: $r = 0.01$, $P = 0.91$). Similar to the ABI, the claudication distance is also inadequate for prediction of TOPP.

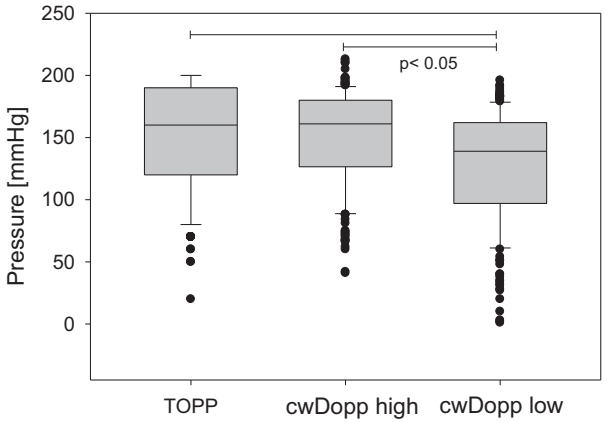


Fig. 5. Tissue optical perfusion pressure (TOPP) vs. high- and low-systolic continuous wave-Doppler (cw-Doppler) pressure of the arteria dorsalis pedis (ADP) and arteria tibialis posterior (ATP). Box plots present median, interquartile range, and 5–95% confidence interval (CI) and outliers (95% CI: TOPP 146, 158.6 mmHg vs. cw-Doppler high 145, 156 mmHg vs. cw-Doppler low 120.5, 133.5 mmHg). Low cw-Doppler systolic pressure is significantly lower than TOPP and high cw-Doppler systolic pressure (*group 1*, $n = 99$: 39 female, 60 male).

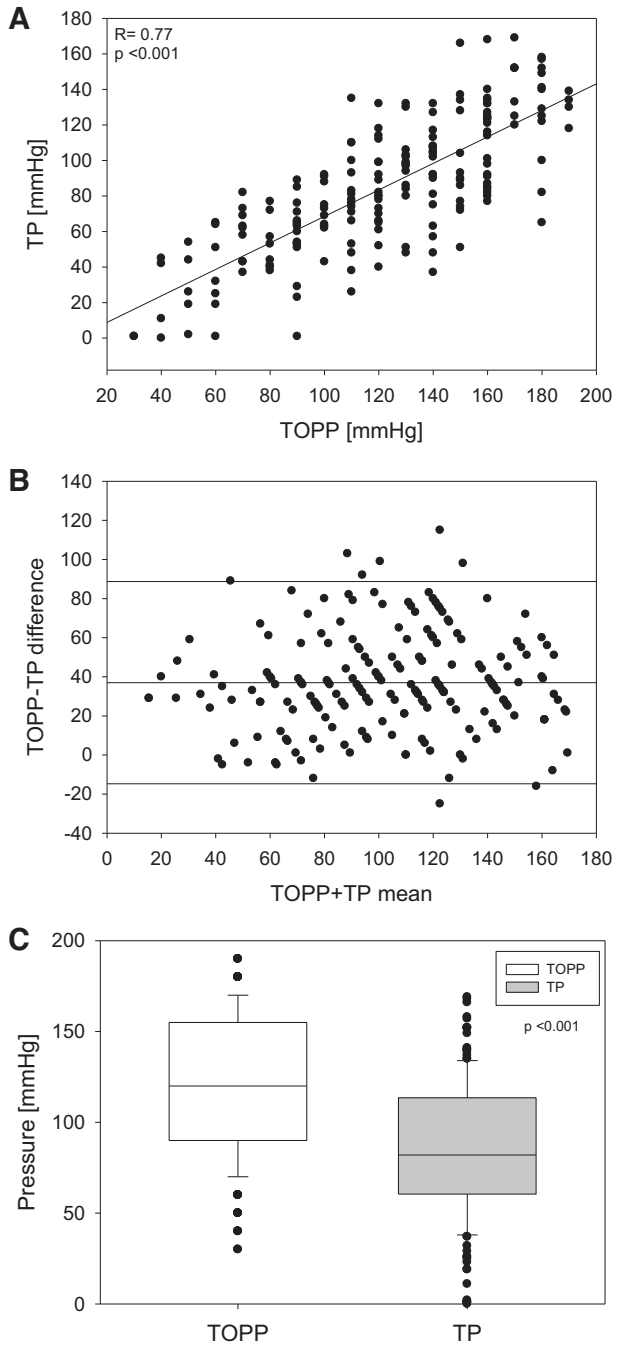


Fig. 6. *A*: regression analysis of tissue optical perfusion pressure (TOPP) vs. toe pressure (TP). *B*: Bland–Altman plot of TOPP vs. TP. Solid lines in graph *B* represent means ± 2× SD. Data present an overestimation of the TOPP in contrast to TP. *C*: TOPP vs. TP. Box plots present median, interquartile range, and 5–95% confidence interval (CI) and outliers (95% CI: TOPP 116.2, 127.4 mmHg vs. TP 79.4, 90.2 mmHg). The absolute difference between TOPP and TP was 37.0 ± 1.88 mmHg (*group 2*, $n = 103$: 40 female, 63 male).

Correlation of TOPP vs. oscillometric ABI. The data of the ABI plotted against the TOPP showed a good correlation at rest ($r = 0.58$, $P < 0.001$; Fig. 7*A*) and a much better correlation after exercise ($r = 0.75$, $P < 0.001$; Fig. 7*B*). There was a significant correlation of TOPP to ABI in patients of *group 3*, with solely flow-limited PAD. In contrast, the correlation of TOPP to cw-Doppler pressure in *group 1* was much better, in which the level of disease was less with low to mild PAD (Table 1).

Correlation of APSV-ATA and APSV-ADP vs. ABI. Mean APSV calculated by the velocity of the distal ATA (APSV-ATA) and ATP was 32.5 ± 1.3 cm/s. By use of the ADP for calculation instead of the distal ATA, APSV-ADP was 30.0 ± 1.3 cm/s. There was no statistically significant difference between both calculations for the APSV-ATA and APSV-ADP (95% CI: 30, 35 vs. 27.5, 32.5, $P = 0.15$).

The ABI at rest presented a low correlation to the APSV-ATA and to a lesser extent to the APSV-ADP (at rest: APSV-ATA $r = 0.31$, $P < 0.001$; Fig. 8*A*; APSV-ADP $r = 0.21$, $P < 0.001$). After exercise, the coefficient of correlation improved for both APSV-ATA and APSV-ADP (after stress: APSV-ATA $r = 0.45$, $P < 0.001$; Fig. 8*B*; APSV-ADP $r = 0.34$, $P < 0.001$). The coefficient of correlation of APSV-ATA was higher in contrast to APSV-ADP.

Correlation of TOPP vs. APSV-ATA and APSV-ADP. TOPP at rest presented a significant correlation to the APSV-ATA and to a lesser extent to the APSV-ADP (at rest: APSV-ATA $r = 0.44$, $P < 0.001$; Fig. 8*C*; APSV-ADP $r = 0.34$, $P < 0.001$).

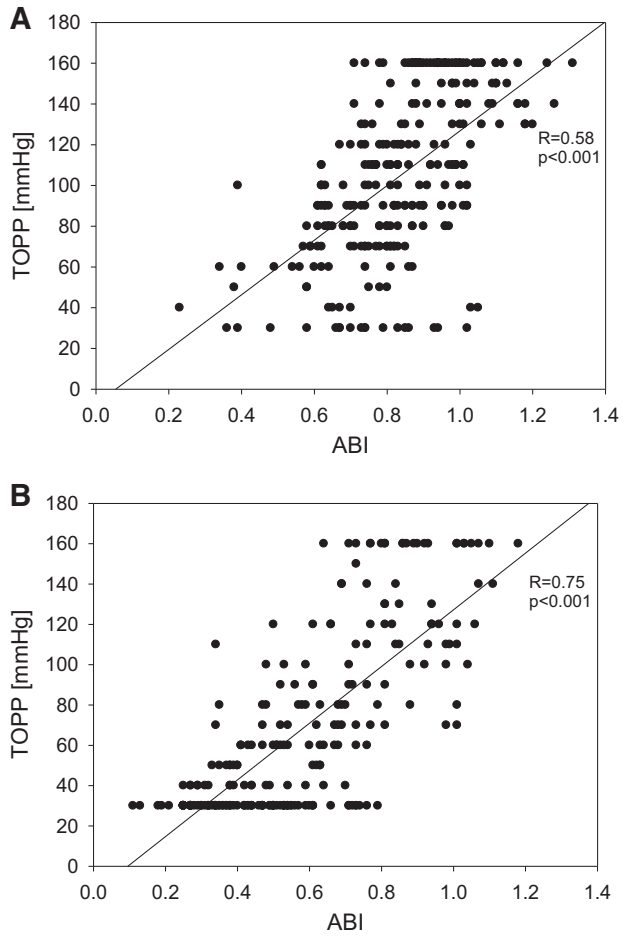


Fig. 7. *A* and *B*: regression analysis of oscillometric ankle-brachial index (ABI) vs. tissue optical perfusion pressure (TOPP) at rest (*A*) and after stress (*B*). Correlation of ABI and TOPP is better after stress, in contrast to ABI at rest (*group 3*, $n = 121$: 43 female, 78 male).

After exercise, the coefficient of correlation did not change substantially for TOPP vs. APSV-ATA and TOPP vs. APSV-ADP (after stress: APSV-ATA $r = 0.47$, $P < 0.001$; Fig. 8*D*; APSV-ADP $r = 0.39$, $P < 0.001$). The r value of APSV-ATA vs. TOPP was better than that of APSV-ATA vs. ABI at rest. Peripheral microcirculation is represented by TOPP rather than by ABI.

Results of Groups 1, 2, and 3

Correlation of total TOPP vs. total oscillometric ABI. Due to the fact that all patients of *groups 1, 2,* and *3* received a complete oscillometric analysis at rest, a regression analysis of all values concerning the simultaneous TOPP ABI measurement between oscillometric ABI and TOPP could be performed. The regression analysis between the oscillometric ABI and the TOPP ($r = 0.65$, $P < 0.001$) was significant.

DISCUSSION

This is the first study in PAD that covered macrocirculation and microcirculation in one and the same examination within 1–2 min time at rest and immediately after exercise testing. The current study showed a significant correlation between the TOPP and the systolic cw-Doppler-pressure on the one hand and oscillometry on the other. The results emphasize the meaning of TOPP as an internal control mechanism of automatic oscillometric ABI measurements. In addition, data are supplied, allowing analysis of tissue perfusion. TOPP provides information of pedal macrocirculation and microcirculation, which cannot be achieved by ABI analysis alone. The oscillometric ABI system used in the present analysis correlated significantly with the reference method of cw-Doppler ABI (*group 1*). In addition, recent data provided an increased sensitivity for detection of PAD using oscillometric ABI in combination with the pulse-wave index (PWI) of the test set used, albeit only at rest (35). Determination of the microcirculation in the toe pad showed a correlation for TP and TOPP; however, the absolute values differed significantly (*group 2*). As a first proof of concept in PAD patients, TOPP combined with oscillometric ABI yielded the opportunity to examine macrocirculation and microcirculation at rest and immediately after stress testing (*group 3*), as required by the Rutherford categories in regard to the Society of Vascular Surgery and the European Society of Cardiology (1, 41, 45, 46). TOPP will provide quantitative measurements of the

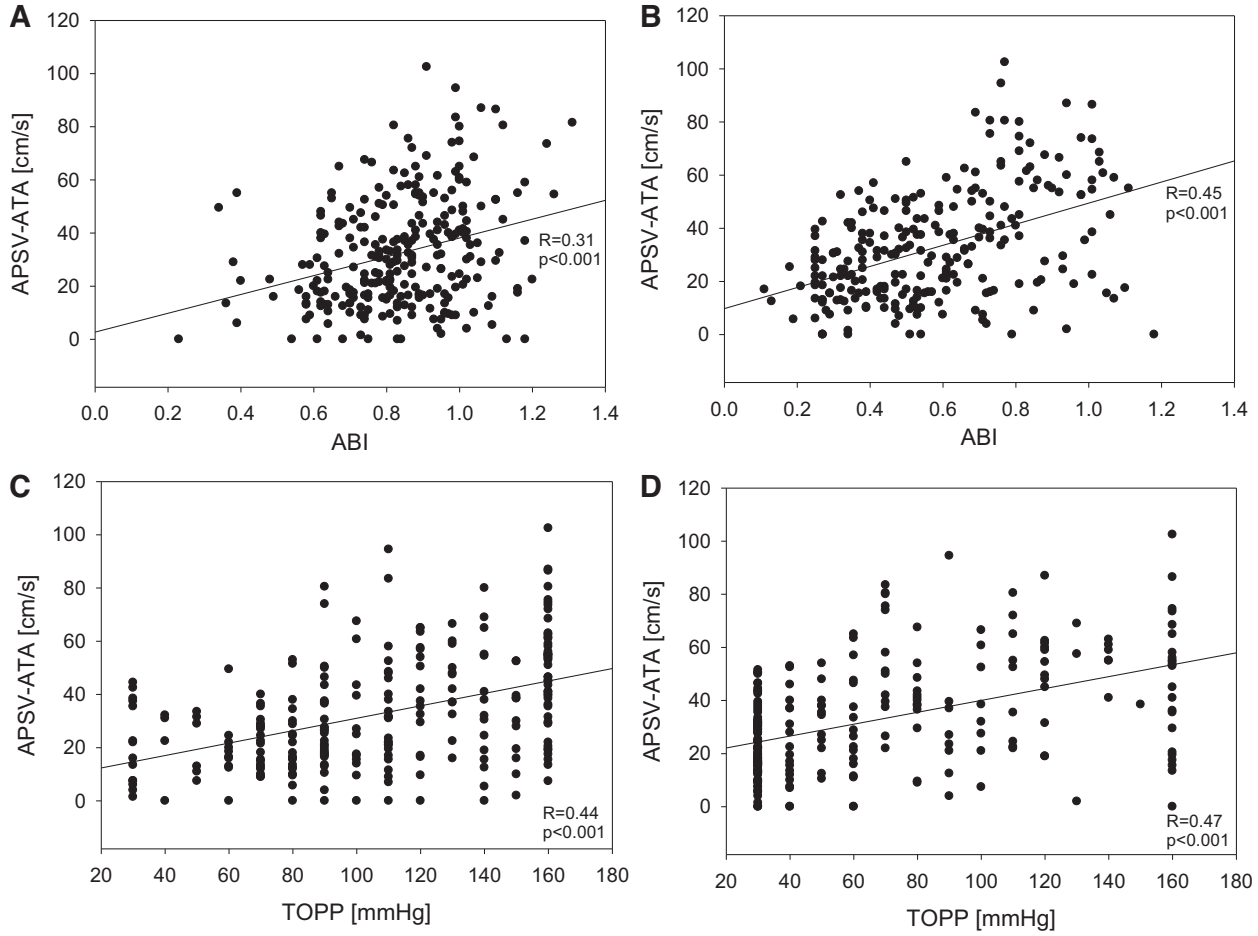


Fig. 8. *A* and *B*: regression analysis of ankle-brachial-index (ABI) vs. ankle-peak systolic velocity of posterior tibial artery at the ankle and distal anterior tibial artery (APSV-ATA) at rest (*A*) and after stress (*B*). *C* and *D*: regression analysis of tissue optical perfusion pressure (TOPP) vs. APSV-ATA at rest (*C*) and after stress (*D*). Correlation of TOPP vs. APSV-ATA at rest is better than that of ABI to APSV-ATA. Correlation is improved after stress (*group 3*, $n = 121$: 43 female, 78 male).

microcirculatory occlusive perfusion pressure at rest and even after stress as well as for follow-up analysis.

The technique of PPG was published in the 1940s, earlier than oscillometry in the late 1950s (17, 22, 26). At first, both techniques were evaluated separately in the 1960s, to be combined later on. As a next step in the development of these methods, cut-off values for the noninvasive determination of patients at risk for PAD were published in the 1970s (5, 12, 13, 37). To evaluate tissue microcirculation in the lower extremities, studies of skin perfusion pressure (SPP) were conducted, and those findings were published in the past (27). SPP is a good assessment of wound healing and of the amputation rate in

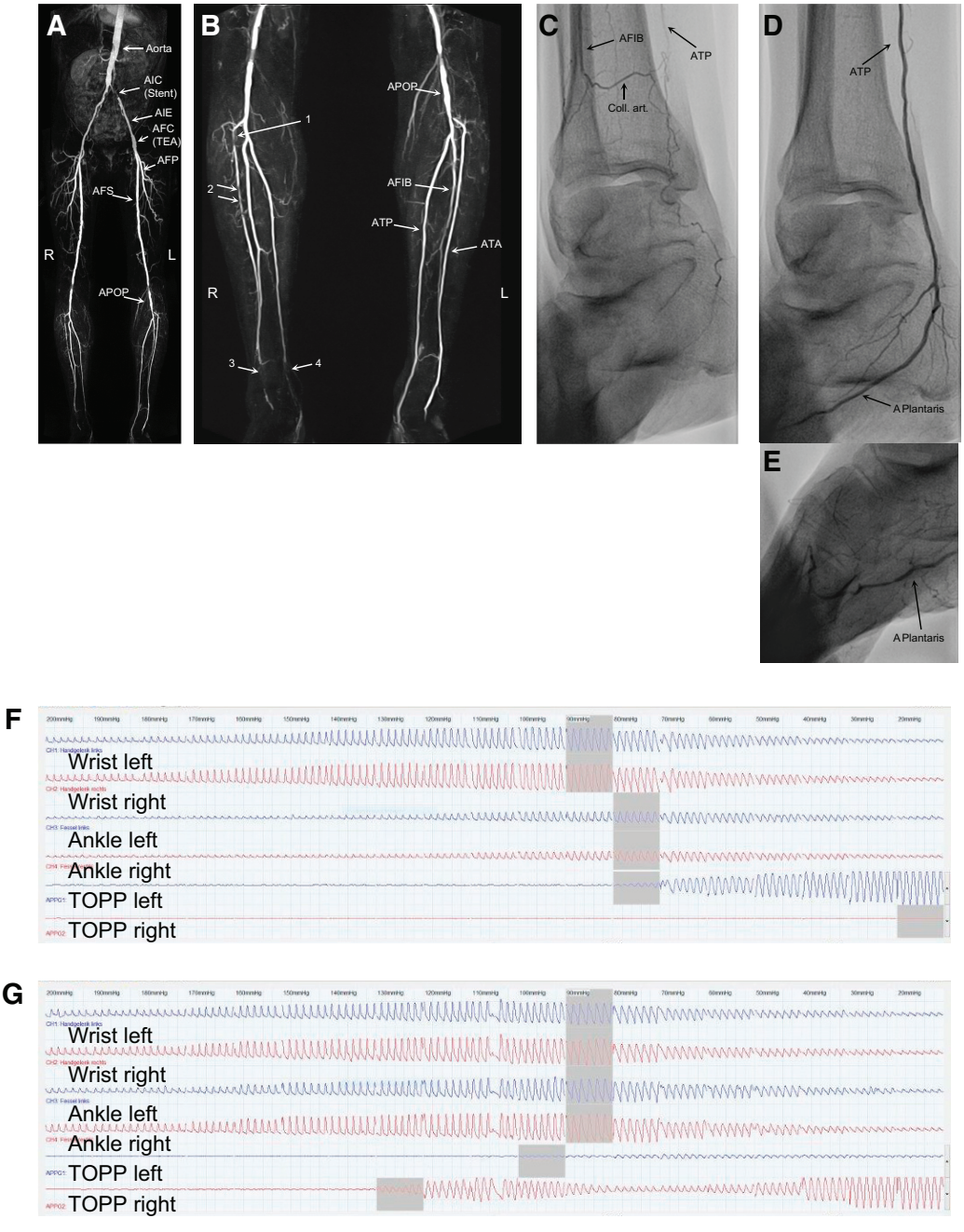


Fig. 9. Example of a patient with peripheral artery disease (PAD) and severely hindered pedal perfusion at the level of the right ankle before and after intervention. *A*: MRI before intervention (AIC, arteria iliaca communis; AIE, arteria iliaca externa;AFC, arteria femoralis communis; TEA: thrombendarteriektomy with patch, AFS, arteria femoralis superficialis; AFP, arteria femoralis profunda; APOP: arteria popliteal). *B*: MRI lower legs before intervention (ATA, arteria tibialis anterior; AFIB, arteria fibularis; ATP, arteria tibialis posterior. *1*: Chronic total occlusion (CTO) of the ATA with collateral arteries; *2*: Stenosis; *3*: ATA-CTO; *4*: ATP-CTO). *C–E*: angiography of distal lower leg and ankle before (*C*, collateral artery from AFIB to ATP) and after recanalization (*D*, ankle; *E*, midplantar). *F* and *G*: tissue optical perfusion pressure (TOPP) ABI at rest before (*F*) and 1 day after intervention (*G*, blue, left wrist/ankle TOPP and red-right wrist/ankle TOPP).

surgery and endovascular therapy in diabetic and nondiabetic patients (2, 15, 21, 48). SPP was primarily determined by radionuclide washout and later by laser Doppler and PPG. The sensors were positioned inside the pressure cuff (27, 28, 33, 50). The idea to place the PPG sensor on the toe and finger pad instead of placing it under or inside the pressure cuff during pressure deflation resulted in the measurement of the toe-finger index (15, 51). The major advantage of our setup consists in the

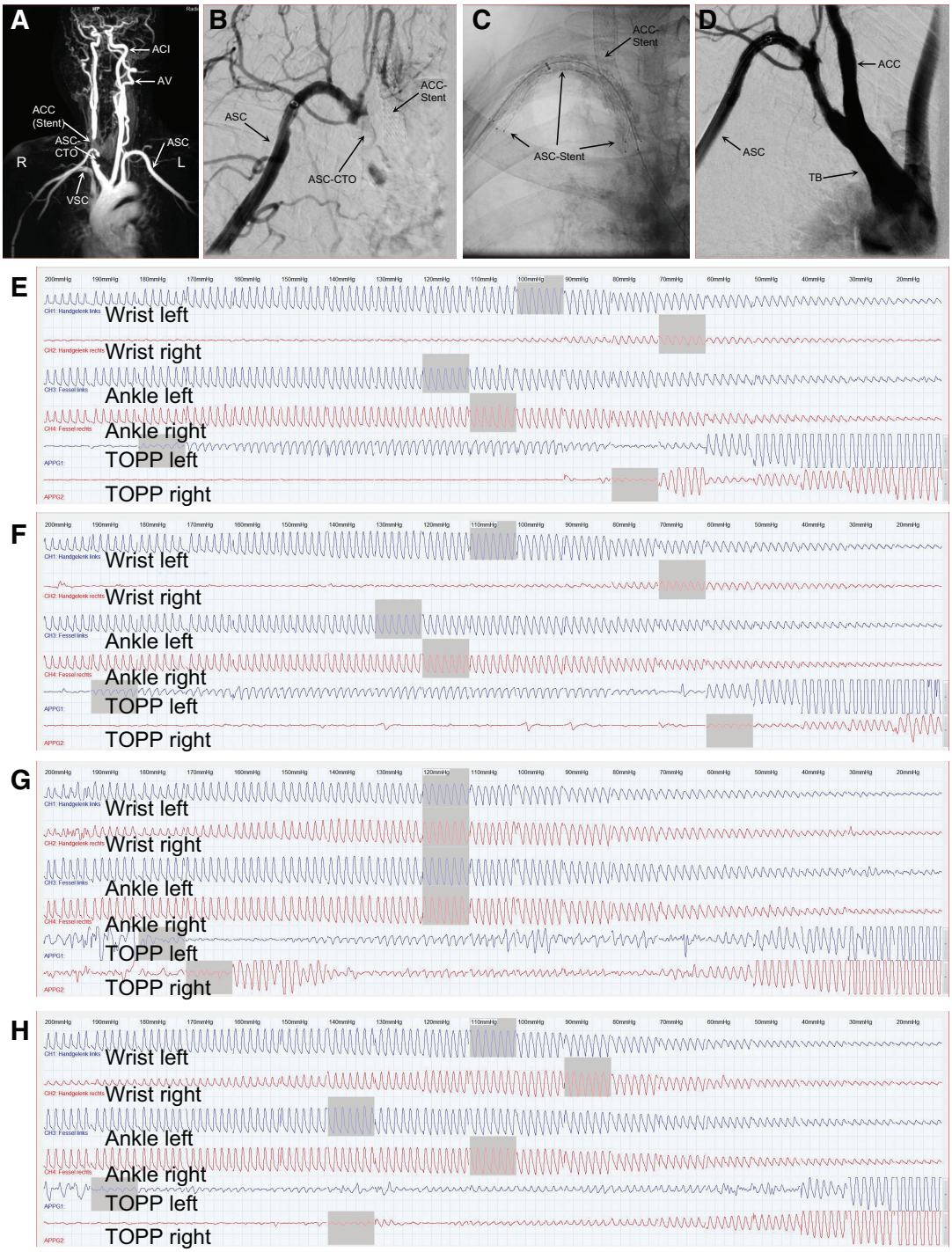


Fig. 10. Example of a patient with subclavian artery occlusion and collateralization before and after intervention. *A*: MRI before intervention (ACC, arteria carotis communis with stent; ASC, arteria subclavia; VSC, vena subclavia, ACI, arteria carotis interna; AV, arteria vertebralis). *B*: digital subtraction angiography (DSA) of the left arm before intervention. *C*: and *D*: DSA after intervention (TB, truncus brachiocephalicus). *E–H*: tissue optical perfusion pressure (TOPP) of the finger pad of the second finger before intervention at rest (*E*) and after stress (*F*) and 4 wk after intervention at rest (*G*) and after stress (*H*).

simultaneous oscillometric and PPG measurement in the sense of a "one-stop-shop" procedure for analysis of macrocirculation and microcirculation. Therefore, we avoid repetitive inflations and deflations, which might induce a hyperemic vascular response. This issue of reproducibility of automatic measuring systems in contrast to handheld systems is supported by previous publications regarding human intraobserver and interobserver variability (36, 40). A single-shot procedure is advantageous compared with an incremental single target vessel measurement (16).

It is difficult to estimate the impact of this new method on PAD examination in the future. However, a definite advantage of TOPP is the identification of patients with solely pedal artery lesions and presenting a normal ABI and decreased TOPP at the toe (Fig. 9). Furthermore, TOPP can detect patients with Raynaud's syndrome, and it can also be used to determine the hemodynamic meaning of subclavian artery stenosis (Fig. 10). Another advantage of TOPP, as it is described in the present setup, is the fact that it can be obtained simultaneously at any location of the foot to analyze and compare different areas of tissue microperfusion. For a standardized and reproducible examination, in our first analysis we used only one PPG channel per foot and placed the sensor on the pad of the first toe. Concerning the variations in anatomy of toe perfusion, in the future it would be of interest to perform a multichannel PPG analysis of each toe, which might be useful in diabetic foot analysis. Local perfusion analysis is even more important, since recent published data have documented that the skeletal muscle dysfunction in early-stage PAD is rather a consequence of limited oxygen supply than of mitochondrial defects (24).

It is a fact that oscillometry detects only the strongest signal of the lower leg arteries above the ankle. The lower cw-Doppler pressure of both major foot arteries (ADP, ATP) will be not considered; therefore, "patients at risk" might be overlooked by automatic oscillometry (20). Looking more closely at the foot artery anatomy, oscillometry at the ankle misses the part of the ADP and ATP below the retinaculum, where stenosis or total occlusions can be found responsible for reduction of pedal perfusion. Pedal microperfusion can also be determined by laser Doppler or MRI (7, 43). These techniques are, on the one hand, time consuming and, on the other hand, difficult to adapt to stress tests for pedal examination and therefore missed in clinical studies (15, 20, 51). TOPP measurement combined with simultaneous ABI analysis solves this issue and provides more insights into pedal microcirculation of PAD patients concerning tissue hemodynamics, especially under stress.

The use of the TP for pedal perfusion is a controversial topic in the literature due to technical aspects (i.e., separate examination, small cuff size, time-consuming examination). Furthermore, the absolute difference in systolic ankle pressure versus TP varies significantly (11, 30). Previous studies reported an absolute difference between TP and systolic ankle pressure of 35–60 mmHg in patients with (rest pain and skin lesions or unhealed ulcers) or without PAD. In addition, the present data confirm the published disagreement (Fig. 6) (11, 14, 21). This study did not present any sex differences.

For an analysis of Fontaine's classification, it is mandatory to perform a clinical stress test to determine ICD and ACD. Both clinical parameters did not correlate with ABI and TOPP. However, TOPP measured immediately after a stress test offers the differentiation of PAD according to the Rutherford classification, especially between classes 2 and 3 (41). Based on the present data, TOPP should be brought to clinical practice as soon as possible. With TOPP plus oszillometric ABI (TOPP-ABI) used as a one-stop-shop screening method, patients with unknown PAD are sooner diagnosed and treated earlier to reduce disease progression.

Limitations

A limitation of the current data analysis is the documentation of the TOPP in 10-mmHg increments. This problem has to be addressed to improve the quality of statistical analysis. However, the results presented have already addressed the potential for clinical use in differentiation of microcirculatory perfusion abnormalities. The limitation of the TOPP should be solved by software improvement.

The anatomy of PAD in the present study includes a wide variety of arterial diseases from very short flow-limiting stenosis to large total occlusion with collateralization of variable effectivity. Another limitation of the study is the missing anatomy and flow distribution of the complete diseased foot arteries, especially the blood supply to the large toe. Therefore, a correlation of TOPP to the plaque location from the MRA or CTA in *group 3* might be inaccurate due to the missing foot artery anatomy. For a detailed analysis, a multichannel TOPP of all toes should be compared with contrast-mediated digital subtraction analysis (DSA) of the foot arteries that could be performed before and after an intervention.

Conclusion

The oscillometric ABI system is as good as a handheld Doppler system for the measurement of ankle-brachial indexes. Moreover, TOPP provides additional insights into pedal macrocirculation and microcirculation. As a first proof of concept in a group of PAD patients, TOPP has shown a correlation to oscillometry as well as to cw-Doppler at rest; however, the correlation was improved after exercise. Prospective sensitivity and specificity studies as well as postinterventional studies should follow.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

G.H. and L.M. conceived and designed research; G.H., A.G. and S.Y. performed experiments; G.H., L.M., A.G., S.Y., G.W. and C.E. analyzed data; G.H., L.M., A.G., S.Y., G.W. and C.E. interpreted results of experiments; G.H., L.M., G.W. and C.E. prepared figures; G.H. drafted manuscript; G.H., L.M., G.W. and C.E. edited and revised manuscript; G.H., L.M., A.G., S.Y., G.W. and C.E. approved final version of manuscript.

REFERENCES

1. **Aboyans V**, **Ricco JB**, **Bartelink ME**, **Björck M**, **Brodmann M**, **Cohnert T**, **Collet JP**, **Czerny M**, **De Carlo M**, **Debus S**, **Espinola-Klein C**, **Kahan T**, **Kownator S**, **Mazzolai L**, **Naylor AR**, **Roffi M**, **Röther J**, **Sprynger M**, **Tendera M**, **Tepe G**, **Venermo M**, **Vlachopoulos C**,

Desormais I; **ESC Scientific Document group.** 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 39: 763–816, 2018. doi:10.1093/eurheartj/ehx095.

2. **Adera HM**, **James K**, **Castronuovo JJ Jr**, **Byrne M**, **Deshmukh R**, **Lohr J.** Prediction of amputation wound healing with skin perfusion pressure. *J Vasc Surg* 21: 823–829, 1995. doi:10.1016/S0741-5214(05)80014-X.
3. **Allen J**, **Murray A.** Comparison of three arterial pulse waveform classification techniques. *J Med Eng Technol* 20: 109–114, 1996. doi:10.3109/03091909609008388.
4. **Allen J**, **Overbeck K**, **Nath AF**, **Murray A**, **Stansby G.** A prospective comparison of bilateral photoplethysmography versus the ankle-brachial pressure index for detecting and quantifying lower limb peripheral arterial disease. *J Vasc Surg* 47: 794–802, 2008. doi:10.1016/j.jvs.2007.11.057.
5. **Ashton H.** Critical closure in human limbs. *Br Med Bull* 19: 149–154, 1963. doi:10.1093/oxfordjournals.bmb.a070035.
6. **Beckman JA**, **Higgins CO**, **Gerhard-Herman M.** Automated oscillometric determination of the ankle-brachial index provides accuracy necessary for office practice. *Hypertension* 47: 35–38, 2006. doi:10.1161/01.HYP.0000196686.85286.9c.
7. **Bierbach B**, **Scheewe J**, **Derfuss T**, **Krug A**, **Schramm R**, **Dahm M**, **Kuroczynski W**, **Kempski O**, **Horstick G.** Continuous regional myocardial blood flow measurement: validation of a near-infrared laser Doppler device in a porcine model. *Microcirculation* 19: 485–493, 2012. doi:10.1111/j.1549-8719.2012.00173.x. .
8. **Bishara RA**, **Taha W**, **Akladious I**, **Allam MA.** Ankle peak systolic velocity: new parameter to predict nonhealing in diabetic foot lesions. *Vascular* 17: 264–268, 2009. doi:10.2310/6670.2009.00032.
9. **Bishara RA**, **Taha W**, **Alfarouk MO**, **Abdel Aal K**, **Wasfy S.** Duplex detected ankle peak systolic velocity: a new parameter for the assessment of degree of peripheralischemia. *Int Angiol* 23: 368–372, 2004.
10. **Bland JM**, **Altman DG.** Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 327: 307–310, 1986. doi:10.1016/S0140-6736(86)90837-8.
11. **Broholm R**, **Wiinberg N**, **Simonsen L.** Measuring systolic ankle and toe pressure using the strain gauge technique—a comparison study between mercury and indium-gallium strain gauges. *Scand J Clin Lab Invest* 74: 555–559, 2014. doi:10.3109/00365513.2014.903431.
12. **Burton AC.** On the physical equilibrium of small blood vessels. *Am J Physiol* 164: 319–329, 1951. doi:10.1152/ajplegacy.1951.164.2.319.
13. **Carter SA.** Indirect systolic pressures and pulse waves in arterial occlusive diseases of the lower extremities. *Circulation* 37: 624–637, 1968. doi:10.1161/01.CIR.37.4.624.
14. **Carter SA**, **Tate RB.** Value of toe pulse waves in addition to systolic pressures in the assessment of the severity of peripheral arterial disease and critical limb ischemia. *J Vasc Surg* 24: 258–265, 1996. doi:10.1016/S0741-5214(96)70101-5.
15. **Castronuovo JJ Jr**, **Adera HM**, **Smiell JM**, **Price RM.** Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia. *J Vasc Surg* 26: 629–637, 1997. doi:10.1016/S0741-5214(97)70062-4.
16. **Congnard F**, **Bruneau A**, **Abraham P**, **Colas-Ribas C**, **Picquet J**, **Noury-Desvaux B.** Time and reliability issues associated with automatic vs. manual measurements of Ankle to Brachial pressure Index (ABI) following heavy load exercise. *J Sci Med Sport* 18: 737–741, 2015. doi:10.1016/j.jsams.2014.10.007.
17. **Delius L.** Beiträge zur pathologischen Physiologie und zur Klinik beginnender Herz-und Kreislaufstörungen (Vergleichende hämodynamische und elektrokardiographische Untersuchungen). *Arch Kreislaufforsch* 11: 1–106, 1942. doi:10.1007/BF02118452.
18. **Diehm C**, **Allenberg JR**, **Pittrow D**, **Mahn M**, **Tepohl G**, **Haberl RL**, **Darius H**, **Burghaus I**, **Trampisch HJ**; **German Epidemiological Trial on Ankle Brachial Index Study group.** Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation* 120: 2053–2061, 2009. doi:10.1161/CIRCULATIONAHA.109.865600.
19. **Emler C**, **Jacomella V**, **Rufibach K**, **Thalhammer C**, **Amann-Vesti BR**, **Husmann M.** Pressure indices in peripheral arterial disease assessed by infrared photosensors. *Angiology* 64: 93–97, 2013. doi:10.1177/0003319712448248.
20. **Espinola-Klein C**, **Rupprecht HJ**, **Bickel C**, **Lackner K**, **Savvidis S**, **Messow CM**, **Munzel T**, **Blankenberg S**; **AtheroGene Investigators.** Different calculations of ankle-brachial index and their impact on cardiovascular risk prediction. *Circulation* 118: 961–967, 2008. doi:10.1161/CIRCULATIONAHA.107.763227.
21. **Faris I**, **Duncan H.** Skin perfusion pressure in the prediction of healing in diabetic patients with ulcers or gangrene of the foot. *J Vasc Surg* 2: 536–540, 1985. doi:10.1016/0741-5214(85)90005-9.
22. **Gesenius H.** Oszillographie und Arteriographie. *Dtsch Med Wochenschr* 74: 1–4, 1949. doi:10.1055/s-0028-1118251.
23. **Working group.** Management of peripheral artery disease. Trans-Atlantic Inter-Society Consensus (TASC). *Int Angiol* 19: 185, 2000.
24. **Hart CR**, **Layec G**, **Trinity JD**, **Le Fur Y**, **Gifford JR**, **Clifton HL**, **Richardson RS.** Oxygen availability and skeletal muscle oxidative capacity in patients with peripheral artery disease: implications from in vivo and in vitro assessments. *Am J Physiol Heart Circ Physiol* 315: H897–H909, 2018. doi:10.1152/ajpheart.00641.2017.
25. **Herráiz-Adillo Á**, **Martínez-Vizcaíno V**, **Cavero-Redondo I**, **Álvarez-Bueno C**, **Garrido-Miguel M**, **Notario-Pacheco B.** Diagnostic accuracy study of an oscillometric ankle-brachial index in peripheral arterial disease: the influence of oscillometric errors and calcified legs. *PLoS One* 11: e0167408, 2016. doi:10.1371/journal.pone.0167408.
26. **Hertzmann AB**, **Spealman CR.** Observations on the finger volume pulse recorded photo-electrically. *Am J Physiol* 119: 334–335, 1937.
27. **Holstein P.** Distal blood pressure as guidance in choice of amputation level. *Scand J Clin Lab Invest Suppl* 128: 245–248, 1973.
28. **Holstein P**, **Lund P**, **Larsen B**, **Schomacker T.** Skin perfusion pressure measured as the external pressure required to stop isotope washout. Methodological considerations and normal values on the legs. *Scand J Clin Lab Invest* 37: 649–659, 1977. doi:10.3109/00365517709100659.
29. **Kornø M**, **Eldrup N**, **Sillesen H.** Comparison of ankle-brachial index measured by an automated oscillometric apparatus with that by standard Doppler technique in vascular patients. *Eur J Vasc Endovasc Surg* 38: 610–615, 2009. doi:10.1016/j.ejvs.2009.07.004.
30. **Kröger K**, **Stewen C**, **Santosa F**, **Rudofsky G.** Toe pressure measurements compared to ankle artery pressure measurements. *Angiology* 54: 39–44, 2003. doi:10.1177/000331970305400105.
31. **Labs KH**, **Nehler MR**, **Roessner M**, **Jaeger KA**, **Hiatt WR.** Reliability of treadmill testing in peripheral arterial disease: a comparison of a constant load with a graded load treadmill protocol. *Vasc Med* 4: 239–246, 1999. doi:10.1177/1358836X9900400406.
32. **MacDougall AM**, **Tandon V**, **Wilson MP**, **Wilson TW.** Oscillometric measurement of ankle-brachial index. *Can J Cardiol* 24: 49–51, 2008. doi:10.1016/S0828-282X(08)70548-8.
33. **Malvezzi L**, **Castronuovo JJ Jr**, **Swayne LC**, **Cone D**, **Trivino JZ.** The correlation between three methods of skin perfusion pressure measurement: radionuclide washout, laser Doppler flow, and photoplethysmography. *J Vasc Surg* 15: P823–P830, 1992. doi:10.1016/0741-5214(92)90717-M.
34. **Mauck GW**, **Smith CR**, **Geddes LA**, **Bourland JD.** The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure–part ii. *J Biomech Eng* 102: 28–33, 1980. doi:10.1115/1.3138195.
35. **Mayr V**, **Hirschl M**, **Klein-Weigel P**, **Girardi L**, **Kundi M.** A randomized cross-over trial in patients suspected of PAD on diagnostic accuracy of ankle-brachial index by Doppler-based versus four-point oscillometry based measurements. *Vasa* 48: 516–522, 2019. doi:10.1024/0301-1526/a000808.
36. **Monti M**, **Calanca L**, **Alatri A**, **Mazzolai L.** Accuracy of in-patients ankle-brachial index measurement by medical students. *Vasa* 45: 43–48, 2016. doi:10.1024/0301-1526/a000494.
37. **Okino H.** Measurement of intraluminal pressure from external pressure with strain transducer. *J Appl Physiol* 19: 546–549, 1964. doi:10.1152/jappl.1964.19.3.546.
38. **Pan CR**, **Staessen JA**, **Li Y**, **Wang JG.** Comparison of three measures of the ankle-brachial blood pressure index in a general population. *Hypertens Res* 30: 555–561, 2007. doi:10.1291/hypres.30.555.
39. **Piepoli MF**, **Hoes AW**, **Agewall S**, **Albus C**, **Brotons C**, **Catapano AL**, **Cooney MT**, **Corrà U**, **Cosyns B**, **Deaton C**, **Graham I**, **Hall MS**, **Hobbs FDR**, **Løchen ML**, **Löllgen H**, **Marques-Vidal P**, **Perk J**, **Prescott E**, **Redon J**, **Richter DJ**, **Sattar N**, **Smulders Y**, **Tiberi M**, **Bart van der Worp H**, **van Dis I**, **Verschuren WMM**; **Authors/Task Force Members.** 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). *Atherosclerosis* 252: 207–274, 2016. doi:10.1016/j.atherosclerosis.2016.05.037.

40. **Richart T**, **Kuznetsova T**, **Wizner B**, **Struijker-Boudier HA**, **Staessen JA.** Validation of automated oscillometric versus manual measurement of the ankle-brachial index. *Hypertens Res* 32: 884–888, 2009. doi:10.1038/hr.2009.125.
41. **Rutherford R**, **Flanigan D**, **Gupta S**, **Johnston K**, **Karmody A**, **Whittemore A**, **Baker J**, **Ernst C**, **Jamieson C**, **Mehta S.** Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. *J Vasc Surg* 4: 80–94, 1986. doi:10.1016/0741-5214(86)90326-5.
42. **Sadiq S**, **Chithriki M.** Arterial pressure measurements using infrared photosensors: comparison with CW Doppler. *Clin Physiol* 21: 129–132, 2001. doi:10.1046/j.1365-2281.2001.00299.x.
43. **Schmitt M**, **Horstick G**, **Petersen SE**, **Karg A**, **Hoffmann N**, **Gumbrich T**, **Abegunewardene N**, **Schreiber WG.** Quantification of resting myocardial blood flow in a pig model of acute ischemia based on first-pass MRI. *Magn Reson Med* 53: 1223–1227, 2005. doi:10.1002/mrm.20457.
44. **Sōpan M**, **Geršak G**, **Millasseau SC**, **Mezōa M**, **Košir A.** Detection of peripheral arterial disease with an improved automated device: comparison of a new oscillometric device and the standard Doppler method. *Vasc Health Risk Manag* 12: 305–311, 2016. doi:10.2147/VHRM.S106534.
45. **Stoner MC**, **Calligaro KD**, **Chaer RA**, **Dietzek AM**, **Farber A**, **Guzman RJ**, **Hamdan AD**, **Landry GJ**, **Yamaguchi DJ**; **Society for Vascular Surgery.** Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. *J Vasc Surg* 64: E1–E21, 2016. doi:10.1016/j.jvs.2016.03.420.
46. **Stoner MC**, **Calligaro KD**, **Chaer RA**, **Dietzek AM**, **Farber A**, **Guzman RJ**, **Hamdan AD**, **Landry GJ**, **Yamaguchi DJ**; **Society for Vascular Surgery.** Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease: executive summary. *J Vasc Surg* 64: P227–P228, 2016. doi:10.1016/j.jvs.2016.03.432.
47. **Takahashi I**, **Furukawa K**, **Ohishi W**, **Takahashi T**, **Matsumoto M**, **Fujiwara S.** Comparison between oscillometric- and Doppler ABI in elderly individuals. *Vasc Health Risk Manag* 9: 89–94, 2013. doi:10.2147/VHRM.S39785.
48. **Utsunomiya M**, **Nakamura M**, **Nagashima Y**, **Sugi K.** Predictive value of skin perfusion pressure after endovascular therapy for wound healing in critical limb ischemia. *J Endovasc Ther* 21: 662–670, 2014. doi:10.1583/14-4675MR.1.
49. **Verberk WJ**, **Kollias A**, **Stergiou GS.** Automated oscillometric determination of the ankle-brachial index: a systematic review and meta-analysis. *Hypertens Res* 35: 883–891, 2012. doi:10.1038/hr.2012.83.
50. **Wahlberg E**, **Gush R.** A new automated toe blood pressure monitor for assessment of limb ischemia. *Eur J Vasc Endovasc Surg* 24: 304–308, 2002. doi:10.1053/ejvs.2002.1664.
51. **Whiteley MS**, **Fox AD**, **Horrocks M.** Photoplethysmography can replace hand-held Doppler in the measurement of ankle/brachial indices. *Ann R Coll Surg Engl* 80: 96–98, 1998.