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Original Communication

Predictive value of a non-invasive assessment of arterial stiffness for identifying undiagnosed coronary artery disease in patients in neurological rehabilitation following their initial ischemic stroke

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ABSTRACT

Knowledge that stroke patients have concomitant coronary artery disease (CAD) is crucial for neurological rehabilitation, because the disease affects the long-term morbidity and mortality of the patients. This knowledge may influence the choice of pharmacological and neurorehabilitation therapies. However, due to the lack of standard routine screening, CAD positive stroke patients often remain unidentified. In this cross-sectional prospective, single-center study we tested a non-invasive screening approach for CAD, employing extracranial color-coded Duplex ultrasound (ECCS) and an oscillatory measurement of arterial stiffness. Overall, significant CAD was tested using bicycle stress electrocardiography (BSE). Patients who had experienced their first stroke but had no history of CAD were examined while in neurological rehabilitation after successful early mobilization. We measured both common carotid arteries to determine intima-media thickness (IMT), presence and extent of plaque, and pulsatility (PI) and resistance (RI) indices. Arterial stiffness was measured using peripheral arterial tonometry (PAT). Of 100 patients (mean/median ages 61/59.2 years; 69 male) in the study, only 14 proved physically able to undergo BSE, and in only 6 patients was ST elevation observed on the baseline electrocardiogram. The IMT was highly correlated with changes in vessel elasticity (RI, PI, and PAT finding) but not with pathological BSE findings, which identified ST elevation in only one patient. Carotid ECCS results correlate with PAT measurements of arterial stiffness, indicating generalized atherosclerosis. Neither method could predict the presence of significant CAD. However, BSE is not the gold standard for CAD detection. Pathological ECG changes were found in fewer patients than expected, indicating a lower risk of CAD than previously reported for other similar patient groups.

KEYWORDS: cardiovascular disease, neurological rehabilitation, stroke, arterial stiffness, carotid artery, intima-media thickness

INTRODUCTION

Patients with coronary artery disease (CAD) and patients who have experienced a stroke share the same cardiovascular-neurovascular risk profile. CAD is well known to be a comorbidity of, or complication after, ischemic stroke [1, 2]. Not surprisingly, patients with a history of ischemic stroke have an abnormally

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high risk for ischemic heart attack [3] and their long-term risk for coronary events is constant at around 2% per year [4]. In addition, the cumulative risk of fatal and non-fatal secondary stroke or fatal cardiac events increases significantly within the first 5 years following stroke [5]. Other studies have shown that 10 years after patients experience an ischemic event, nearly half will face another vascular event, and approximately 30% will develop other vessel diseases such as myocardial infarction, other coronary events, or vascular death unrelated to the stroke [6, 7]. As early as 1991, Salonen and Salonen reported that the relative hazard of a coronary event depends on the intima-media thickness (IMT) and rises if the carotid artery contains plaque or is stenotic [8]. This study was conducted at the National Public Health Institute of Finland with the aim to identify the risk of developing CAD after a first stroke and it revealed a correlation between carotid arterosclerosis and the increased CAD rate. With this information in place a plan can be pursued for long-term benefit from rehabilitative therapy. The study group consisted of patients who had experienced their first ischemic stroke but had no diagnosis of CAD.

In the recent years our impression was that CAD risk significantly dropped in our first time stroke patients. Thus, we examined patients immediately after admission to neurological rehabilitation and again after they were mobile (once they could move around or walk, had stable cardiopulmonary function, and had no acute infection). Since our neurological rehabilitation clinic has no invasive cardiology department, we chose non-invasive techniques to assess vascular parameters and screen for significant CAD. Specifically, we employed bicycle stress electrocardiography (BSE) for this purpose. Extracranial color-coded sonography (ECCS) and peripheral arterial tonometry (PAT), two non-invasive techniques that can be used to assess generalized vascular disease, were used to predict future CAD.

We hypothesized a significantly lower rate of first time stroke rehabilitation patients with high CAD risk and investigated the correlation between CAD and morphological characteristics of blood vessels observed on sonograms, flow properties of the common carotid artery (that is, the IMT, resistance index (RI), pulsatility index (PI), and presence and extent of plaque), and arterial stiffness, which would allow non-invasive identification of stroke patients at risk for future coronary events.

MATERIALS AND METHODS

The study protocol was approved by the local ethics committee at the University of Regensburg in accordance with the Declaration of Helsinki (No. 11-101-0175). We examined patients who had experienced their first ischemic stroke and been admitted to a German hospital for neurological rehabilitation. All patients were recruited between October 2011 and December 2012. Participating patients had been admitted to a 'Phase D' rehabilitation unit for mobile patients [9] in physically stable condition and were deemed capable of performing a BSE. A score of at least 60 points on the Barthel Index is a prerequisite for entry into Phase D neurorehabilitation [10, 11]. Exclusion criteria included a known history of CAD, inability to perform the BSE, presence of cognitive impairments or aphasia that would significantly impair understanding of instructions, no written informed consent, and a clear stroke etiology unrelated to arteriosclerosis (for example, vessel dissection or vasospasm after subarachnoid hemorrhage). We used a modified version of the Essen Stroke Risk Score [12] to assess the risk of cardiovascular events in general; to meet study eligibility a summed score of 3 or higher was required. We added items such as known CAD and body mass index (BMI) to screen the population, but excluded 'other cardiovascular event' and 'known transient ischemic attack/stroke' because these criteria were already part of the study inclusion criteria.

Extracranial color-coded sonography

Ultrasonographic examinations were performed using a standard color-duplex ultrasound system equipped with a linear-array transducer (5-8 MHz) for the extracranial examination (GE Vivid 7, GE Wauwatosa, WI, USA). First, standard extracranial color-coded duplex sonography (ECCS) was used to evaluate atherosclerotic lesions or plaque in the anterior supra-aortic circulation. Measurements of peak systolic (PSV), end diastolic (EDV), and mean blood flow (MFV) velocities in the bilateral common carotid arteries (CCAs) were obtained. Briefly, after optimization of the transmit frequency and power, focal zone, and pulse repetition frequency, the color gain was adjusted to guarantee good-quality

measurements of parameters of interest. We then obtained the PIs and RIs of the bilateral common carotid arteries [13]. The RI was automatically calculated by using the following formula: RI = (PSV – EDV)/PSV; and the PI was determined using a formula described in the literature: PI = (PSV – EDV)/MFV [14]. The inner and outer diameters of the left and right CCAs were measured after the systolic phase. Finally, the GE Vivid 7 ultrasound system was used to obtain an optimal measurement of IMT; this was done automatically with manual correction if needed. IMT was measured for vessels on both sides at a site about 1 cm distal to the carotid bulb and over a distance of approximately 3 cm. Illustrative examples are given in Figures 1 and 2.

B-Mode ultrasonography of the carotid artery

We matched the structure and macroscopic aspects of the tunica intima and tunica media of the carotid artery wall, inspecting both the common carotid artery and internal carotid bulb walls with cross sectional ultrasound as exemplified in Figure 3, to classify the grade of arteriosclerosis between 1 and 6 (Table 1). We inspected and classed lime content, unevenness and the grade of intima-media destruction to describe the presence and

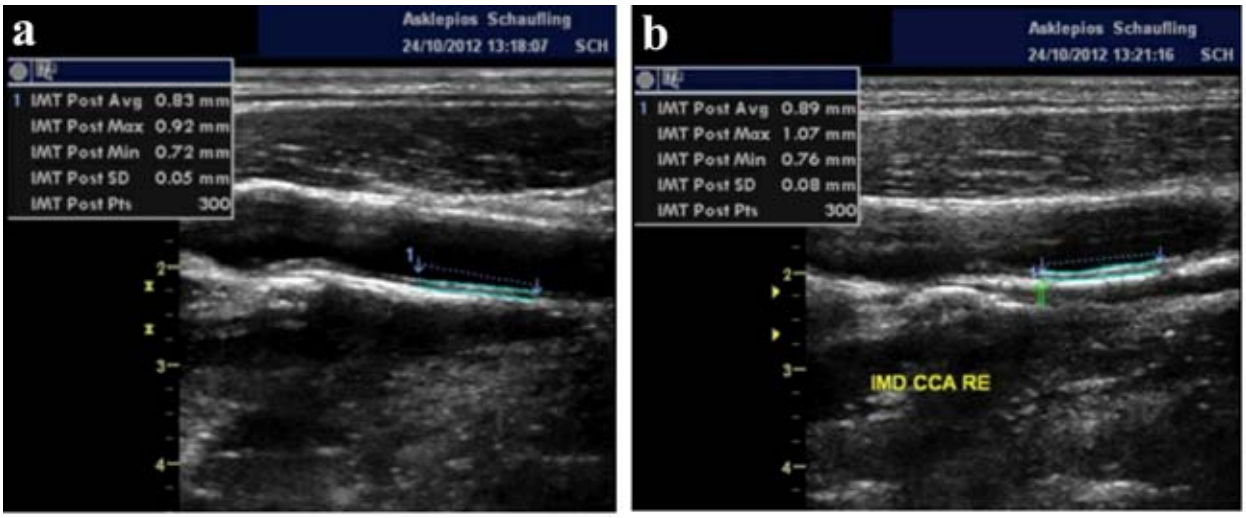

Figure 1. a) Left-sided and b) right-sided measurements of intima-media thickness (IMT) obtained in the same patient. Measurements begin 1 cm proximal to the carotid bulb and extend 3 cm.

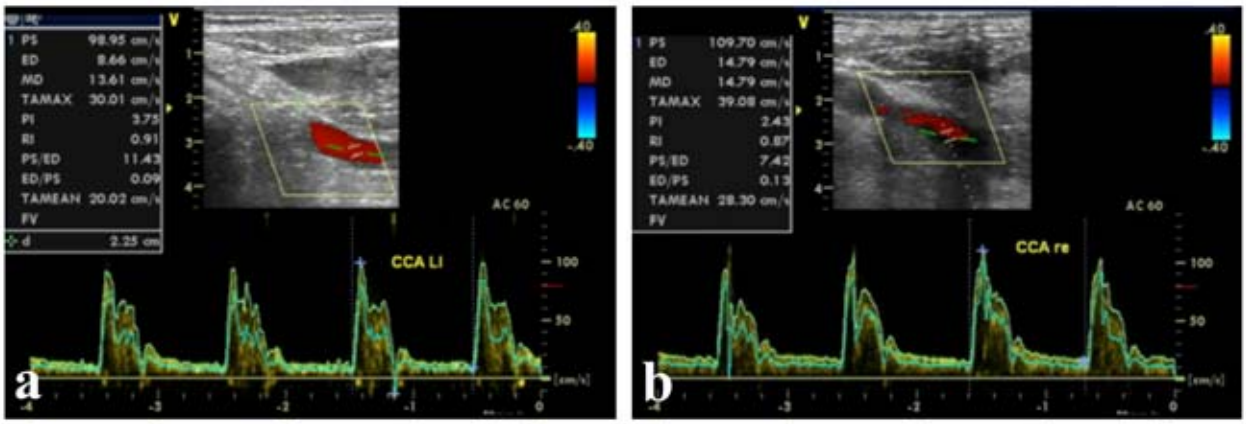

Figure 2. a) Left-sided and b) right-sided resistance and pulsatility indices (RIs and PIs) obtained in the same patient.

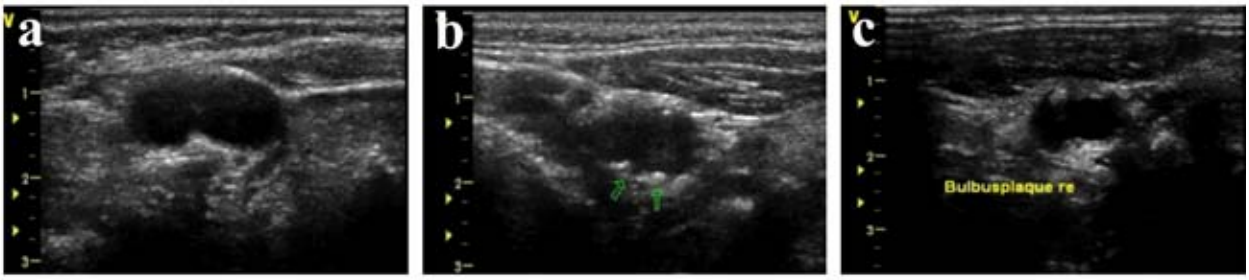

Figure 3

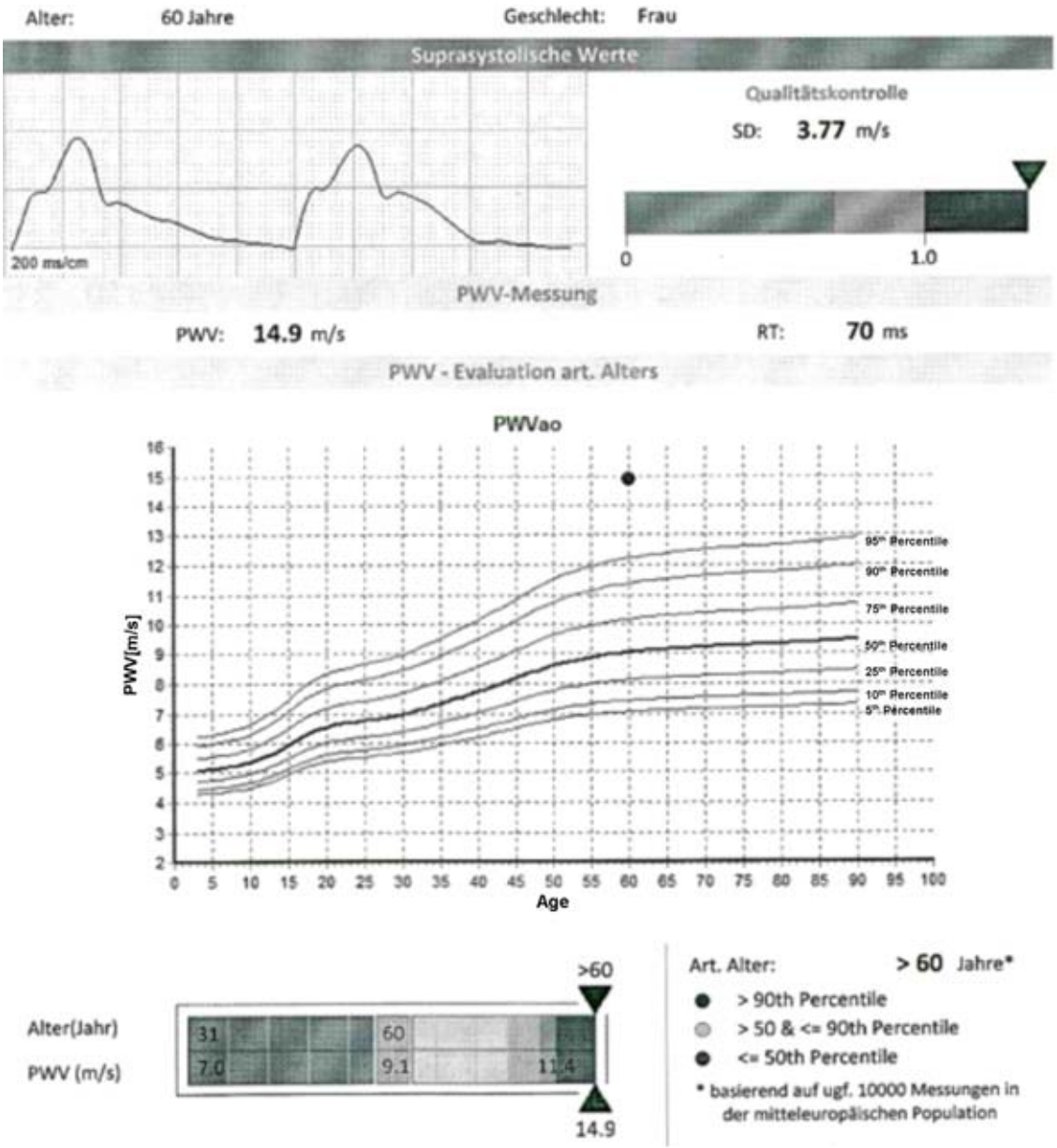

Figure 4

extent of plaque in accordance with the grade of arteriosclerosis, referring to the Ultrasound carotid measurement and following Post-Mortem Analysis of Wada in the early 90s [15]. To compare the grade of arteriosclerosis with arterial stiffness, the pulse wave velocity (PWV), which is a good indicator of arterial stiffness, was compared to those defined classes [16, 17].

Peripheral arterial tonometry

Peripheral arterial tonometry (PAT; Arteriograph™, TensioMed®, Budapest, Hungary) allows for a non-invasive measurement of arterial stiffness and an analysis of systolic and diastolic blood pressures. It detects the direct systolic wave, the reflected wave for the aortic bifurcation, and the diastolic waves. The device has an upper arm cuff that includes a sensory unit quite similar to those used for automated measurements of systolic and diastolic blood pressure. PAT adjusts the pressure of the upper arm cuff to approximately 35 mm Hg above systolic pressure. It measures blood pressure, including changes therein, and self-adjusts several times over systolic pressure. All suprasystolic pressure changes are recorded. To calculate the Aorta pulse wave velocity (PWVao), we measured the distance from the sternal notch to the upper edge of the pubic bone. Based on data from the literature, this represents a valid estimation of aortic length [17]. The PWVao was calculated using the following formula: PWVao (m/s) = distance (in meters) between the jugulum and symphisys/ (reflection return time (in seconds)/2. PAT also measures the aortic augmentation index (Aix). The Aix aortic is a parameter that reflects the degree to which central arterial pressure is enhanced by wave reflection of the pulse wave [16]. This was calculated using the following formula: Aix (%) = $(P_2 - P_1 / PP) \times 100$, whereby P_2 is the amplitude of the reflected systolic pulse wave, P_1 is the amplitude of the direct systolic pulse wave, and PP is the pulse pressure. The PWV and the Aix (which describes the influence of the reflected pulse wave as it relates to systolic pressure) are used to describe arterial stiffness and endothelial/ vascular dysfunction [16, 17, 18, 19, 20]. An example is illustrated in Figure 4.

Bicycle stress electrocardiography

To determine whether CAD is present, we used a WHO-approved 25-W standard test of physical working capacity (PWC test) for patients with reduced physical working capacity. Before the bicycle stress electrocardiography (BSE), each patient underwent a clinical examination including electrocardiography (ECG) with direct signal recording afforded by an ECG-based chest strap (Polar Electro GmbH Deutschland, Büttleborn, Germany). No patient with abnormal ECG findings was allowed to undertake the BSE test. If a patient received beta-blocker medication, we suspended this medication 3 days before the planned BSE test. Treatment with beta blockers was resumed after the study ended. We used an electronically guided bicycle ergometer (Ergometrics 900, Ergoline GmbH, Bitz, Germany) with an ECG-based integrated pulse measurement system. Stress was incrementally increased in 25-W steps, starting with 25 W, in accordance with a software-based WHO protocol. The test ended as soon as maximal or submaximal stress was reached or at subjective exhaustion. If the regularly scheduled end of the test could not be reached, the reason for premature termination was recorded. The normal test duration was 15 minutes, with the last measurement obtained 6 minutes after maximal or submaximal stress had been reached. Measurements included heart rate (HR) and systolic and diastolic blood pressures. To account for age differences,

Legend to Figure 3. Representative ultrasound images showing three classes of carotid medial thickness based on the stratification presented in Table 1 (all coronal section) at the level of carotid bifurcation.
a) Vessel with regular intima-media structure. Classified as ‘even 1’.
b) Vessel with focal hyperechoic plaques protruding into the lumen. Classified as ‘uneven 1’.
c) Vessel with multiple hyperechoic irregular plaques. Classified as ‘uneven 2’.

Legend to Figure 4. Peripheral arterial tonometry (PAT) results in a 60-year-old woman. The aortic pulse wave velocity (PWVao) reached 15.8 m/s, corresponding to serious arteriosclerotic vessel disease as compared to age related normal values. Image, lower left corner: upper row - age in years; lower row - PWV in m/sec. The measured PWV of 14.9 m/sec exceeds the normal value at this age by more than 50%.

we used 3 variations of the PWC test. For patients younger than 30 years and physically strong persons, the maximum PWC was 170; for persons between 31 and 50 years, the maximum PWC was 150; and for persons 50 years and older, and for physically weak persons older than 40 years, the maximum PWC was 130 [21, 22, 23, 24].

RESULTS

Study population

One hundred patients were included in our study. The mean (± SD) age in these patients was 60.6 ± 9.8 years, and 69% (69/100) were male. The mean BMI (± SD) of the population was 20.5 ± 4.51, and 47% of patients had known carotid artery sclerosis. Only one person had known peripheral artery disease, whereas 85 suffered from arterial hypertension. The prevalence of diabetes mellitus type 2 in this cohort was 29%, while 48% of patients were smokers.

Extracranial color-coded sonography (ECCS) and PAT data

We classified vessel wall structure in the CCA as it appears on ECCS by using the macroscopic classification shown in Table 1. The descriptive analysis shows a reasonable coherence between macroscopic aspects of the vessel observed via the duplex B-mode and their effect on arterial stiffness [8, 15, 16, 17, 18, 19, 20, 25]. Our data did not reveal a positive correlation between pathological conditions of the vessel wall (assessed by determining the IMT, RI and PI, plaque content and extent, and arterial stiffness) and pathological findings on bicycle stress electrocardiograms. Statistical analysis showed no correlations between BSE results (e.g. BSE termination or finish) and our measurements of IMT, macroscopic aspects of the CCA (plaque and stenosis), and arterial stiffness. Measurements of IMT showed occasional negative correlations (Pearson) at a level of 0.05 (2-sided). In addition, no positive significance was found when we compared the RI and PI with the BSE loading. No correlation was found between the measured vessel wall and the BSE loading (no positive significance, Pearson 2-sided: 0.05) or between arterial stiffness and the BSE loading. However, the sonographic characterization of the vessel wall and the assessment of arterial stiffness correlated well and confirmed generalized vascular pathology. We used the Spearman correlation coefficient to analyze plaque morphology on an ordinal scale and found

Table 1. Grade of carotid artery sclerosis found using Duplex sonography.

Grade of atherosclerosis	Structural aspect of medial thickness		IMT min (mm)	IMT max (mm)	PWV min (m/s)	PWV max (m/s)	% of Study group
1		even 1	0.5-0.8	0.44-1.18	7.5	16.9	20
2		even 2	0.6-1.1	0.76-1.76	7.5	15.8	34
3		even 3	0.5-0.9	0.84-1.54	6.6	13.1	23
4		partially uneven	0.6-1.0	0.92-1.42	8.6	13.2	12.0
5		uneven 1	0.7-2.0	1.05-3.05	8.7	18.3	9.0
6		uneven 2	0.8	1.24-1.27	10.9	10.9	2

Classification of B-Mode depiction of structures related to artherosclerosis grades (1-6). We matched structures and other macroscopic aspects of the tunica intima and tunica media, inspecting both CCAs and carotid bulbs to categorize the grade of artherosclerosis from 1 to 6. In this manner we described and classified the presence and extent of plaque according to the grade of artherosclerosis. The graphics shown in the column 'Structural aspect of medial thickness' are modified, self-drawn adaptations for sonographic images in this study based on Wada's "Grading criteria for histological classification of common carotid artherosclerosis" [15].

significant (Pearson 2-sided: significance set at 0.05) or highly significant (Pearson 2-sided: significance set at 0.01) correlations. Our prediction was, of course, a highly significant correlation between age and ongoing arteriosclerosis, and we found this. We also found some negative significance concerning the BMI (Table 2). We identified a higher brachial augmentation index in women than in men in our patient population by applying Mann-Whitney U-tests (Table 3). In addition, as expected, we found greater arterial stiffness in patients with hypertension, patients with diabetes, and active smokers (Tables 4-6). There was no difference between known or unknown carotid arteriosclerosis (Table 7).

Bicycle stress data

Data obtained from the BSE test were not usable in our clinical setting. Exclusion criteria were angina pectoris, dyspnoea and exhaustion. Also high blood pressure (systolic > 200 mmHg, diastolic > 110 mmHg) before bicycle stress electrocardiography, missing increase in blood pressure as well as an abnormal drop or increase in blood pressure during BSE (over 230-260 mmHg systolic or 115 mmHg diastolic blood pressure) led to the termination of BSE. Furthermore, we excluded supraventricular tachycardia, brady-arrhythmia, AV-Blockade, and ST-distance lowering in ECG recording. All measured data were derived from the lead-ECG and blood pressure measurements during the BSE. For safety reasons, close medical observation by our experienced cardiologist was present to detect exhaustion or ongoing cyanosis while performing BSE [23]. Thus, only 14 patients completed a BSE workout. At the end of the study, the BSE was prematurely terminated in the other 86 patients. The only significance finding was between hypertension and premature termination of the BSE test (Table 8).

Table 2. Correlation between patient age and BMI.

		Aix brachial	Aix brachial 75	Aix aortic	Aix aortic 75	PWV	SBPao	RT
Age	Pearson correlation coefficient	0.445**	0.360**	0.448**	0.188	0.299**	0.399**	–0.374**
	Significance (2-sided)	0	0.002	0	0.118	0.003	0	0
	N	95	70	94	70	100	96	99
BMI	Pearson correlation coefficient	–0.251*	–0.209	–0.189	–0.274*	0.045	0.201*	0.069
	Significance (2-sided)	0.014	0.083	0.068	0.022	0.659	0.05	0.5
	N	95	70	94	70	100	96	99

**Correlation is significant at the level of 0.01 (2-sided).
*Correlation is significant at the level of 0.05 (2-sided).
We found a good correlation between advancing age and weight gain in our study population.
Aix brachial (%) = $(P_2 – P_1 / PP) \times 100$. Describes the impact of reflected pulse wave to the systolic pressure (mural reflection of brachial artery, % of pulse pressure). It correlates strong with endothel-dysfunction and artherosclerosis. The Aix is decisive for the aortal blood pressure.
Aix aortic (%)
Same like Aix brachial, referring to mural aortic reflection.
PWV = Pulse Wave Velocity (m/s).
SBPao (mmHg)
Central systolic blood pressure near aortic root, ‘Cardial afterload’.
RT = ‘reflection time’ (ms).
Duration of the pulse wave from the aortic root to the bifurcation and back.

Table 3. Correlation between gender and arterial stiffness.

	Aix brachial	Aix brachial 75	Aix aortic	Aix aortic 75	PWV	SBPao	RT
Mann-Whitney U	296	333	295.5	328	550.5	513	614.5
Wilcoxon W	2711	1558	2641.5	1553	2965.5	2928	1110.5
Z	–5.017	–2.327	–4.974	–2.391	–3.87	–3.41	–3.318
Asymptotic significance (2-sided)	0	0.02	0	0.017	0	0.001	0.001

Group variable: gender.
Significant and highly significant differences in arterial stiffness between women and men.
We found significant and highly significant differences between women and men. Higher values for the Aix brachial ($p < 0.001$) were found in women, and the mid-range in women (71.12) was clearly higher than the mid-range in men (39.29).

Table 4. Correlation between hypertension and arterial stiffness.

	Aix brachial	Aix brachial 75	Aix aortic	Aix aortic 75	PWV	SBPao	RT
Mann-Whitney U	413	287	400.5	286	452	307	355.5
Wilcoxon W	504	378	491.5	377	572	412	3925.5
Z	–1.299	–1.261	–1.38	–1.277	–1.792	–2.772	–2.68
Asymptotic significance (2-sided)	0.194	0.207	0.168	0.202	0.073	0.006	0.007

Group variable: hypertension.
In part we found significant differences for people with hypertension. In our study population hypertension was related to increased arterial stiffness.

Table 5. Correlation between diabetes mellitus type 2 and arterial stiffness.

	Aix brachial	Aix brachial 75	Aix aortic	Aix aortic 75	PWV	SBPao	RT
Mann-Whitney U	580	399	580	414	839.5	933	859.5
Wilcoxon W	986	652	958	667	3395.5	1368	1265.5
Z	–2.922	–1.632	–2.712	–1.443	–1.444	–0.307	–1.045
Asymptotic significance (2-sided)	0.003	0.103	0.007	0.149	0.149	0.759	0.296

Group variable: diabetes mellitus type 2.
In part we found a significant difference between patients suffering from diabetes mellitus type 2 and those without the disease.

Table 6. Correlation between history of cigarette smoking and arterial stiffness.

	Aix brachial	Aix brachial 75	Aix aortic	Aix aortic 75	PWV	SBPao	RT
Mann-Whitney U	778.5	423	778	422.5	1043	784	920
Wilcoxon W	1859.5	1053	1813	1052.5	2219	1865	2298
Z	–2.595	–2.226	–2.456	–2.232	–1.415	–2.684	–2.117
Asymptotic significance (2-sided)	0.009	0.026	0.014	0.026	0.157	0.007	0.034

Group variable: cigarette smoking.
Significant differences were apparent for the Aix brachial/Aix brachial 75, Aix aortic, SBao, and RT. Cigarette smoking caused increases in arterial stiffness in our study population. But there was no significant difference in PWV between patients who smoked cigarettes and those who did not.

Table 7. Correlation between known history of carotid sclerosis and arterial stiffness.

	Aix brachial	Aix brachial 75	Aix Aortic	Aix Aortic 75	PWV	SBPao	RT
Mann-Whitney U	1113	584	1092.5	559.5	1109.5	1072	1049
Wilcoxon W	2388	1364	2127.5	1339.5	2540.5	2107	2177
Z	–0.089	–0.242	–0.076	–0.532	–0.94	–0.554	–1.213
Asymptotic significance (2-sided)	0.929	0.808	0.94	0.595	0.347	0.579	0.225

Group variable: known carotid sclerosis.
We found no difference in arterial stiffness between patients with a known history of carotid sclerosis and those with no such history.

Table 8. Premature termination of bicycle stress test in cases of hypertension (valid cases = 100).

	Value	Asymptotic significance (2-sided)	Exact significance (2-sided)	Exact significance (1-sided)
Pearson Chi-Square Test	9.908[a]	0.002		
Yates Correction[b]	7.53	0.006		
Likelihood-Ratio Test	7.769	0.005		
Fisher Exact Test			0.006	0.006
Coherence linear-to-linear	9.809	0.002		

[a]One cell (25.0%) shows expected frequency to be less than 5. The minimal expected frequency is 2.10.
[b]Yates correction for continuity can only be calculated for a 2 × 2 table.
Hypertension causes increased termination of the PWC bicycle stress test before completion.
We found a clear connection between premature termination of the bicycle stress test and the presence of hypertension ($p = 0.002$). Patients with hypertension quit the PWC bicycle stress test before completion more often than those without hypertension.

DISCUSSION

Main findings

Findings of the current study cannot support the use of BSE to identify subclinical CAD in stroke patients in rehabilitation, because there was a lack of positive correlation between vessel wall pathologies (as shown by IMT, increased RI and PI, presence and extent of plaque, and arterial stiffness) and pathological findings on bicycle stress electrocardiograms. Nevertheless, both sonographic characterization of the vessel wall and the assessment of arterial stiffness correlated well and confirmed generalized vascular pathology. In general, the presence of CAD in our study population was lower than expected from the literature, as was the ability of patients to participate in BSE.

Stroke and CAD

The risk of myocardial infarction following a patient's initial stroke is the subject of a variety of studies [8, 26]. Indeed, after the initial stroke, patients often experience other relevant vessel diseases [5, 27, 28]. Early in the 1990s, the Oxfordshire Community Stroke Project showed that following a patient's first stroke, the overall risk of death within the first 30 days is 19% and the risk in the first year is 31% [2]. Indeed, between 6 months and 6 years after the initial stroke, cardiovascular death is the main cause of death [2]. However, the Oxfordshire Community Stroke Project did not discriminate between lacunar stroke syndromes and territorial ischemic insults. In the present study, we only examined patients at the most advanced phase of neurological rehabilitation (Phase D). To qualify for advanced phases of rehabilitation, these patients' levels of disability and, probably, those of comorbity were lower than those of patients in the Oxfordshire study. In addition, that investigation was a community-based study with the goal of predicting long-term outcome for up to 6.5 years.

The PRECORIS study included 3 years' follow-up in patients between the ages of 45 and 75 years who had suffered non-disabling, non-cardioembolic ischemic stroke or transient ischemic attack (TIA) and had no history of CAD. In that study, the prevalence of asymptomatic CAD was 18%, which may be closer to that in our study patients [29]. The coronary risk in patients with TIA or ischemic stroke is well known [5, 30]. In 2005 in a meta-analysis of 65,996 patients, Touzé and colleagues found that 'patients with TIA or stroke have a relatively high risk of MI and non-stroke vascular death' [27]. In an evaluation of coronary risk in patients with 'stroke' or 'other vascular causes', conducted by the American Heart Association in 2003, the late mortality rate after the initial stroke event was between 29% and 45% [31]. In that study the short-term risk in patients in whom there was no known CAD was low, and the authors believed that evaluation of all patients after stroke or TIA may not be justified. Our goal was to identify a subgroup of patients with a higher risk of CAD by employing an easy non-invasive approach involving BSE, ultrasonography of the CCA, and measurement of arterial stiffness. It is noteworthy to mention that patients in Phase D rehabilitation often suffer from lacunar syndromes and that the underlying small vessel disease is attributed to severe hypertension. Adams *et al*. found that "atherosclerosis is invariably the cause of CAD ... but likely subtypes of ischemic stroke related to underlying atherosclerosis (e.g. carotid/vertebral/intracranial stenosis) are associated with a higher risk of CAD than are non-atherosclerotic subtypes of stroke" [31]. In patients with the subtype of stroke that we examined, ischemic carotid artery stroke, we were unable to identify a risk of CAD by employing BSE.

After the initial stroke, our patients generally underwent diagnostic examination in the acute-care hospital (especially in the stroke unit), and well-defined cardiac and vascular diagnostic tests were conducted before the patient was transferred to the rehabilitation facility. As a consequence, nearly no additional CAD was revealed in our study. All study patients regularly finished neurological rehabilitation with a definite neurological improvement, and more important, none died. Finally, in the past years, the quality of stroke therapy offered during the acute phase in German hospitals has dramatically increased with the introduction of telestroke networks such as the TEMPiS [32]. In addition to appropriate and rapid stroke therapy, which is provided in internal medicine departments and supplemented with telemedicine, advancements in diagnosis and treatment of CAD, which is even more familiar to internal medicine, may be relevant.

IMT, presence and extent of plaque, arterial stiffness, and CAD

In 2011 Amarenco *et al*. [3] reported the presence of coronary plaque in 61.9% (193/315) of patients after the initial stroke. These researchers found that the number of coronary plaques increased when both plaque in the carotid artery and peripheral arterial disease were present. Common risk factors (advancing age, gender, high BMI, hypertension, diabetes, dyslipidemia, smoking, and familial history of stroke or CAD) have been analyzed as independent cardiovascular risk factors. The presence of coronary plaque has been significantly associated with the presence of plaque in the carotid and femoral arteries [3]. These analyses in patient groups following initial stroke were the basis for our study design. In 2006 Cheng and colleagues showed that clinical care following ischemic stroke was significantly inferior to that given to patients with CAD [33]. In 2010 Reynolds *et al*. demonstrated a close correlation between IMT and the presence of CAD, and concluded that a normal IMT measurement on carotid ultrasonography nearly excludes the presence of CAD [25]. On the other hand, the 2010 Carotid Atherosclerosis Progression Study did not find IMT in the carotid artery clinically useful for developing a risk classification [34]. For that reason, we included measurement of arterial stiffness in addition to ultrasound examination of the CCA. Measurements of arterial stiffness and determination of the elastic characteristics of blood vessel provide sensitive and valid tools to assess arteriosclerotic vessel disease, because arterial stiffness is known to correlate with the overall atherosclerotic disease burden [16]. It has been shown that the Aix and an accelerated PWV correlate highly with a high cardiovascular risk. The PWV is known to be significantly [35]. The Aix is a reliable and valid risk predictor for further cardiovascular risk prediction [36]. The relationship between CCA thickness and stages of atherosclerosis was investigated by a post-mortem analysis of ultrasound-measured CCA stiffness in 1994. In that study, conducted by Wada *et al*., atherosclerosis grade correlated well with wall thickness [15]. The authors showed that the grade of atherosclerosis and plaque could reasonably predict the thickness of the tunica media and tunica intima, the grade of destruction of the intimal elastic membrane, and therefore the increase in arterial stiffness [15]. We found a good correlation between the grade of arteriosclerosis found using ultrasound sonography and both IMT and arterial stiffness.

Limitation of the study

Diagnostic tests performed in acute-care hospitals to identify significant CAD may be very successful in limiting the number of undiagnosed patients who enter Phase D neurological rehabilitation. Known CAD led to the exclusion of at least four patients from this study (data not shown). The effectiveness of diagnostic tests may be responsible for the fact that in our study fewer patients had CAD after their initial stroke than expected based on earlier reports in the literature. Another limitation is that the BSE with the required (sub-) maximum PWC was performed in only 14 (14%) of the 100 patients in this study. Many reasons for the premature termination of the BSE were identified. The majority (86%) of patients did not reach their maximum PWC because they suffered from excess hypertension. Other reasons for premature termination of the BSE include exhaustion in 39%, pain in 11%, and shortness of breath in 10% of patients. The ultrasound investigation was also limited in some patients due to vascular disease-related problems such as dilatative angiopathy, carotid bifurcation near the skull base, and kinking, among others; thus measurements could only be obtained over shorter distances than the planned distance of 3 cm.

CONCLUSION

We found a high percentage of patients in Phase D neurological rehabilitation who were unable to perform the BSE. As a consequence, BSE in neurological rehabilitation clinics is not a suitable method to detect the presence of CAD. Measuring IMT during carotid ultrasonography is an effective means to evaluate arterial stiffness, as the results of carotid ECCS and PAT correlated well. As the present study was underpowered due to the low number of patients completing the BSE test, further studies are needed to define the value of ultrasound investigations of the carotid arteries (esp. IMT-measuring) and PAT as a screening tool of CAD after stroke. Other methods for detection of CAD have to be discussed in the future. For example,

coronary artery calcium scans or troponin blood serum levels in concert with measurement of the IMT should be evaluated. As of yet, carotid ECSS and PAT alone were not able to detect CAD. The low rate of pathological ECG changes may predict a lower risk of CAD in our study population than reported previously in other studies.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest related to this study.

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