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Carotid artery wall stiffness is increased in patients with small vessel disease: A case-control study

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SUMMARY

Introduction Cerebral ischemic small-vessel disease (SVD), causing lacunar infarcts and white matter hyperintensities on brain magnetic resonance imaging (MRI), is a progressive disease associated with an increased risk of stroke, dementia and death. Increased arterial stiffness has been associated with ischemic stroke and cerebral SVD independently of common vascular risk factors.

Objective The aim of the study was to analyze arterial stiffness in our patients with symptomatic SVD.

Methods In a cross-sectional study design we included 30 patients with clinical and MRI evidence of cerebral SVD and 30 age-, gender- and risk factor-matched control subjects with no neurological diseases. Patients were evaluated at the Ultrasound Laboratory at the Neurology Clinic, Clinical Center of Serbia in Belgrade, during a three-month period (from September 1st to December 1st 2012). Baseline demographic and vascular risk factors were recorded. All patients underwent standard carotid ultrasound scans with measuring of intima-media thickness (IMT) and analysis of atheromatous plaques. Internal carotid artery stiffness was evaluated with the use of e-tracking option as beta stiffness index (BSI) value.

Results There were no differences between study groups in regard to degree of carotid stenosis and type of carotid plaques ($p>0.05$). Patients in SVD group had significantly higher mean IMT ($p=0.0093$) and mean BSI ($p<0.0001$) than subjects in the control group. No significant correlation was detected between IMT and BSI in SVD group ($r=0.168$; $p=0.376$). Brain lesions severity correlated with BSI ($r=0.733$; $p<0.0001$).

Conclusion Arterial stiffness is increased in symptomatic patients with SVD, independently of vascular risk factors and IMT.

Keywords: carotid artery; intima-media thickness; arterial stiffness; beta stiffness index

INTRODUCTION

Cerebral ischemic small-vessel disease (SVD), causing lacunar infarcts and white matter hyperintensities on brain magnetic resonance imaging (MRI), is a progressive disease associated with an increased risk of stroke, dementia and death [1]. Aging and arterial hypertension have been identified as major risk factors for ischemic SVD, but underlying mechanisms are not fully elucidated [2]. Recently, increased arterial stiffness has been associated with ischemic stroke and cerebral SVD independently of common vascular risk factors [3]. E-tracking, a new ultrasound software modality, is increasingly used to assess carotid artery distensibility during cardiac cycle with continuous ECG monitoring [4]. Pathological arterial stiffness, expressed as a beta stiffness index (BSI) higher than 6, has been reported as a marker of early atherosclerosis and an indicator of vascular aging [5, 6].

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OBJECTIVE

The aim of the study was to analyze arterial stiffness in our population of patients with symptomatic cerebral SVD.

METHODS

In a prospective cross-sectional study design we included 30 patients with clinical and MRI evidence of cerebral SVD and 30 age-, gender- and risk factor-matched control subjects with no neurological diseases, evaluated at the Ultrasound Laboratory at the Neurology Clinic, Clinical Center of Serbia in Belgrade, during a three-month period (from September 1st to December 1st 2012). Baseline demographic and vascular risk factors were recorded [7]. All patients underwent standard carotid ultrasound scans, performed by trained ultrasonologists blinded for clinical data, comprising color triplex examination of cervical segments of carotid and vertebral arteries in a standard manner [8]. Degree of carotid stenosis expressed in percentage of diameter reduction, Mannheim criteria for intima-media thickness (IMT) and atheromatous plaques analysis were performed in all subjects [8, 9]. Carotid artery stiffness evaluation was done with the use of e-tracking option in a standard manner (probe of 7.5 to 14 MHz, Aloka Alpha-10, Hitachi, Tokyo, Japan) [3, 4], and expressed as mean BSI values after two bilateral measurements [10]. Artery stiffness is calculated as BSI which is derived from regional diameter and blood pres-

sure change. Measurements are performed in a standard manner, in supine position with head elevation of up to 45° and side tilt of 30° to the right and then to the left [4]. B-mode IMT measurements are done subsequently 1.5 cm proximally to the flow divider on the distal wall of CCA bilaterally in diastole over three to five cardiac cycles, systolic and diastolic inter-adventitial excursions are noted and results are expressed as arithmetic means automatically [4]. Prior to arterial stiffness examination, patients are advised to avoid caffeine beverages and have a rest period of at least 10 minutes. Severity of lesions attributed to SVD (confluent white matter lesions and lacunar infarctions) was expressed through age-related white matter changes (ARWMC) score as reported previously [7]. The study has been approved by the Ethics Committee of the Clinical Center of Serbia.

The results are tabulated. Statistical analysis included a description statistics and use of Fisher's exact probability test, χ^2 and ANOVA for testing the differences between groups. Pearson's correlation coefficient was determined in order to test association between selected variables. The value of $p<0.05$ was considered statistically significant.

RESULTS

Both study groups were comparable in terms of age, gender and common vascular risk factors (Table 1). Hypertension was the most frequent risk factor in both groups, followed by hyperlipidemia and active smoking. Mean ARWMC score was 10.2±3.7 for the SVD group.

Ultrasound characteristics of both study groups are shown in Table 2. No statistically significant difference was detected in regard to IMT and beta-index values between right and left side in both study groups, so mean values for both sides were included in further analysis. Patients with SVD had mildly increased IMT compared to normal value, while it was normal in control subjects. Also, IMT values in the SVD group were significantly higher compared to the control group (p=0.0093). Carotid stenosis was mild in all participants (<50% diameter reduction) (Table 2). Mean carotid stenosis values did not differ between study groups (Table 2). No statistically significant difference was noted in plaque quality between the SVD and the control group, although echolucent plaques were more frequent in SVD patients. In the SVD group mean BSI values were significantly higher than in the control group (p<0.0001) (Table 2).

Analysis of correlation between risk factors and BSI showed only statistically significant correlation between hypertension and BSI in SVD patients (r=0.560; p=0.0013). No other statistically significant correlation was detected for any of the risk factors, including age, both in SVD and control group.

No statistically significant correlation was detected between IMT and beta-index values (r=0.168; p=0.376) in the SVD group. However, correlation between severity of SVD lesions (ARWMC score) and BSI was excellent (r=0.733; p<0.0001).

Table 1. Demographic characteristics and vascular risk factors in both study groups

Characteristics	Number of patients (%)		p-value
	SVD group (n=30)	Control group (n=30)	
Age (years)	63.1±12.7*	60.0±13.5*	0.310
Male gender	7 (23.3)	10 (33.3)	0.567
Hypertension	23 (76.7)	18 (60.0)	0.267
Diabetes mellitus	1 (3.3)	2 (6.7)	0.999
Hyperlipidemia	18 (60.0)	14 (46.7)	0.438
Atrial fibrillation	2 (6.7)	1 (3.3)	0.999
Coronary artery disease	7 (23.3)	4 (13.3)	0.506
Peripheral artery disease	0 (0.0)	1 (3.3)	0.999
Smoking	9 (30.0)	13 (43.3)	0.422
Alcoholism	2 (6.7)	4 (13.3)	0.671
Previous TIA	4 (13.3)	2 (6.7)	0.671

* mean ± SD

SVD – small vessel disease; TIA – transient ischemic attack

Table 2. Carotid ultrasound characteristics in both study groups

Characteristics	SVD group	Control group	p-value
IMT (mm)	1.07±0.21#	0.91±0.25#	0.0093*
Carotid stenosis	18.3±20.3#	10.7±18.7#	0.134
Plaque quality	Echogenic in 10, echolucent in 4, mixed in 2	Echogenic in 7, mixed in 1	0.339
Beta-index	7.2±2.2#	5.3±1.0#	<0.0001*

mean ± SD; * statistical significance p<0.05
SVD – small vessel disease; IMT – intima-media thickness

DISCUSSION

We report results of the first pilot study in our population analyzing new ultrasound modality, e-tracking, as a tool to evaluate carotid artery wall stiffness. Results of this case-control study show that carotid artery BSI is significantly increased in our symptomatic patients with SVD, indicating affections of both small and large arteries. Although SVD patients typically have mild atherosclerotic changes on carotid and other large arteries, there is evidence of widespread pathological process of the arterial wall, expressed both through increased BSI and IMT values. Since both large and small artery disease share common vascular risk factors, it is still not elucidated why some patients dominantly develop one and some another type of vessel involvement.

Undoubtedly aging and vascular risk factors contribute to changes of arterial elasticity and distensibility [3, 4]. As previously reported, hypertension is one of the most important risk factors for pathological arterial stiffness, which has been shown in our study as well [3-6]. We did not detect correlation between age and other risk factors with BSI in any of the groups. Assessment of arterial stiffness is increasingly used as an index of hypertension-related cardiovascular target organ damage and considered to be an independent predictor of cardiovascular events and cardiovascular mortality in patients with different comorbidities and cardiovascular risk [5, 11]. Tsivgoulis et al. [12] found that both carotid IMT and increased stiffness were significant predictors of occurrence of ischemic

stroke, independently of conventional vascular risk factors. Also, increased arterial stiffness was associated with stroke independently of IMT values [12].

Our findings are in accordance with several previous reports. Notably, we found strong correlation between ARWMC score expressing severity of brain lesions attributable to SVD, and BSI values. Poels et al. [13] found that increased aortic wall stiffness in patients with SVD was associated with larger white matter lesion volume, but not with lacunar infarcts or microbleeds. Similarly, a French study reported an association between increased carotid stiffness and larger white matter hyper intensity volumes and increasing prevalence of lacunar infarcts on MRI scans [14].

Interestingly, we did not find an association between IMT and BSI, which has also been reported [12]. This implies different underlying pathological changes, indicating that arterial stiffness and atherosclerosis may be secondary to independent processes involved in the pathogenesis of cerebrovascular disease, but occurring at similar sites in the artery. Increased arterial stiffness can be viewed as an intermediate factor in the causal pathway between the risk factors and a stroke. Some authors suggested that genetic factors may play important role by contributing to differences in the structure of connective tissue in the arterial wall, which partly determines the arterial stiffness [12, 15].

Singer et al. [16] conducted a systematic review of the evidence associating arterial stiffness with cognitive function and cognitive decline with markers of cerebral SVD. They concluded that arterial stiffness is associated with cerebral SVD and decreased cognitive function but also emphasized the problem of methodological differences between studies [16]. Since our study had cross-sectional design and included only SVD patients who already had clinically evident symptoms of the disease, it is not possible to determine temporal relationship between changes in arterial stiffness, IMT alteration and SVD evolution. Therefore, future research should focus on BSI analysis in early, asymptomatic phases of SVD. Early selection of patients at particular risk of developing symptomatic SVD could alter primary prevention strategies in highly susceptible subpopulation of patients and possibly improve their prognosis.

CONCLUSION

Carotid artery arterial stiffness is altered in symptomatic patients with SVD indicating affection of both large and small vessels, independently of vascular risk factors and increased IMT. With the use of appropriate ultrasound software, arterial stiffness can be easily and noninvasively assessed. Clinical implications of this finding are yet to be determined but may add to understanding of pathogenetic processes involved in SVD.

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Чврстоћа зида каротидне артерије је повећана код особа са болешћу малих крвних судова мозга: анамнестичка студија

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КРАТАК САДРЖАЈ

Увод Болест малих крвних судова (БМКС) мозга доводи до лакунарних инфаркта и хиперинтензитета беле масе на магнетној резонанцији (МР) мозга. Ово је прогресивна болест удружена с повећаним ризиком од можданог удара, деменције и смрти. Повећана чврстоћа зида артерија удружена је са исхемијским можданим ударом и БМКС независно од других васкуларних фактора ризика.

Циљ рада Циљ студије је био да се анализира чврстоћа зида артерија код болесника са симптоматском БМКС.

Методе рада У студији пресека укључено је 30 болесника с клиничким и МР доказима БМКС и 30 контролних испитаника без неуролошког обољења упарених по годинама, полу и факторима ризика. Болесници су евалуирани у Ултразвучном кабинету Клинике за неурологију Клиничког центра Србије у Београду током три месеца (од 1. септембра до 1. децембра 2012). Записивани су основне демографске карактеристике и васкуларни фактори ризика. Сви болесници су подвргнути стандардном каротидном ултразвучном прегледу са мерењем интима-медијалног комплекса (ИМТ) и анализом атеромских плакова. Чврстоћа зида унутрашње каротидне артерије процењена је коришћењем опције електронског праћења (тзв. *e-tracking* опција) као вредности бета индекса чврстоће (БСИ).

Резултати Нису уочене разлике између група у погледу степена каротидне стенозе и врсте каротидног плака ($p>0,05$). Испитаници БМКС групе имали су статистички значајно већу просечну вредност ИМТ ($p=0,0093$) и БСИ ($p<0,0001$) него испитаници контролне групе. Није утврђена статистички значајна корелација између ИМТ и БСИ у БМКС групи ($r=0,168$; $p=0,376$). Тежина лезија беле масе је била у корелацији са БСИ ($r=0,733$; $p<0,0001$).

Закључак Чврстоћа зида артерија је повећана код болесника са симптомима обољења БМКС независно од васкуларних фактора ризика и величине ИМТ.

Кључне речи: каротидна артерија; интима–медија комплекс; чврстоћа артерије; бета индекс

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