Systemic Endothelial and Arterial Changes in Migraineurs: A Review of Literature

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Abstract
Migraine is a common, primary, chronic-intermittent neurovascular headache disorder that is a risk factor for developing cardiovascular diseases and stroke. Recent methodological approaches for measurement of arterial or endothelial function have been advanced. Endothelial dysfunction and arterial changes could be evaluated by non-invasive techniques. These non-invasive methods include ultrasound examination, arterial tonometry, plethysmography and magnetic resonance angiography. Whether migraineurs had abnormal findings of endothelial dysfunction and the arterial changes in the cranial and the peripheral artery system has been debated in previous literature. Herein we aimed to introduce widely used non-invasive techniques to measure vascular function, and also to review the literature of endothelial function and arterial findings in migraine patients.

INTRODUCTION
Migraine is a common, primary, chronic-intermittent neurovascular headache disorder. Many previous studies suggested that migraine could be a risk factor for developing cardiovascular disease (CVD) or stroke. CVD and ischemic stroke was noted in migraineurs [1-3]. Vascular changes traditionally seem to disrupt cranial blood vessels during migraine attack [4]. In addition to the involvement of the cranial circulation, systemic vascular dysfunction has been reported during a migraine attack or at the interictal period in migraineurs [5-7]. The aims of this review are to introduce common and useful non-invasive techniques to measure arterial or endothelial function in humans, and also to summarize the main literature of systemic endothelial function and arterial elasticity in migraineurs.

Non-invasive tests of endothelial or arterial function
Recently, many methodological approaches have been developed to measure arterial or endothelial function in humans. Endothelial dysfunction and arterial changes could be evaluated using non-invasive tests [9-10]. These non-invasive methods include ultrasound, applanation arterial tonometry of the brachial artery, finger plethysmography and brain magnetic resonance angiography (MRA).

At first, flow-mediated dilation (FMD) of the brachial artery is the most common technique to measure endothelial function on ultrasound examination. The technique measures the diameter of the brachial artery and the arterial changes during reactive hyperemia after a 5-minute occlusion of the brachial artery with a blood pressure cuff [10,11]. Finger plethysmography is another tool for measurement of endothelial function using peripheral arterial tonometry. The device has been developed to measure observer-independent pulsatile arterial volume changes [12,13]. Applanation arterial tonometry is used the most widely for measurement of arterial elasticity. Pulse wave velocity (PWV) and augmentation index (AIx) are expressed as the parameters of arterial stiffness. FMD indicates functional status of the endothelium whereas PWV and AIx are more related to structural changes of the arterial wall. PWV reflects segmental arterial elasticity. Contraction of the left ventricle generates a pulse wave which is propagated throughout the arterial system. PWV is calculated as the distance traveled by the pulse wave divided by the time taken to travel the distance [10,14,15]. Increased arterial stiffness is associated with high propagation speeds of the pulse wave in the artery. PWV can be measured in any arterial segment between 2 pulse-wave palpable regions (carotid and femoral or brachial and ankle) [10,15]. The assessment of carotid-femoral arterial PWV (cfPWV) rather than brachial-ankle PWV (baPWV) is more relevant the risk of cardiovascular disease. cfPWV is the gold standard of assessment, but it is difficult to measure.
In clinical practice, it can be replaced by the measurement of baPWV even if this measurement includes elastic and muscular arteries. Alx is a marker related to the stiffness of the arterial system [10,16-18]. A reflected pulse wave (from the periphery to the heart) generates at the sites of an abrupt increase in arterial resistance, such as arterial branching. The interaction between the incident pulse wave (from the heart to the periphery) and the reflected pulse wave (from the periphery to the central region) is assessed by pulse wave analysis and shown as the Alx. PWV and peripheral reflectance are important determinants for Alx [10,16-18].

Endothelial function tests in migraineurs

FMD of the brachial artery: FMD of the brachial artery was the most common study of endothelial function in migraineurs [7,18-25]. Results of FMD studies were not consistent. Several studies supported reduction of FMD in migraineurs [6,7,19-21]. Other studies showed normal endothelial function. There were no significant differences of FMD between migraineurs and control subjects [22-25]. We described previous studies of normal and abnormal FMD in chronological order.

Abnormal FMD in migraineurs: Following five studies suggested abnormal FMD in migraineurs [6,7,19-21]. De Hoon et al. reported the first examination using ultrasound and applanation tonometry [7]. Several cardiovascular properties were compared between migraine patients and control subjects. Vascular parameters of the carotid artery, cardiac output and systemic vascular resistance did not differ between both groups. Right temporal artery diameter was larger in migraine patients. Migraine patients displayed a smaller distension and a decreased compliance in the brachial artery. Thus, migraine patients display an increased peripheral arterial stiffness.

In the study by Yetkin et al., FMD and nitrate-mediated dilatation of the brachial artery were measured in 24 migraine patients and 26 control subjects. FMD was significantly lower in migraineurs compared to control subjects. However, nitrate-mediated dilatation was significantly higher in migraineurs than that of controls. Thus, migraineurs decreased endothelium-dependent function and increased nitrate-mediated response in the brachial artery [6].

Vanmolkot et al. performed arterial function tests in 50 patients with recent onset of migraine patients and 50 age and sex-matched control subjects. Brachial artery diameter and compliance were decreased in migraine patients compared to controls. Femoral artery compliance was decreased in migraine patients. Carotid arterial wall properties were similar between migraineurs and controls. FMD of the brachial artery was decreased in migraine patients. Thus, arterial function was altered in migraineurs of recent onset [19].

The study by Vernieri et al. showed FMD in 21 migraineurs (10 MA patients and 11 MO patients) and 13 control subjects. FMD was expressed by measuring the percentage increase of the brachial artery diameter induced by hyperemia reactive to sustained cuff inflation around the arm above systolic pressure. FMD values were normalized for shear stress. Normalized FMD values were higher in MA patients compared to controls and MO patients. Thus, MA patients had an excessive arterial response to hyperemia [20].

Jiménez Caballero et al. examined FMD of the brachial artery, using finger plethysmography, in 21 patients with chronic migraine and 21 healthy controls. Brachial artery FMD was decreased in migraineurs compared to healthy controls. Chronic migraineurs have endothelial dysfunction in the peripheral artery [21].

No significant changes of FMD in migraineurs: Following four studies addressed normal FMD of the brachial artery in migraineurs [22-25]. Silva et al. reported FMD in 50 migraineurs and 25 healthy subjects matched by gender and age. The endothelial function is not altered during the interictal period in migraineurs [22]. In the study by Vanmolkot et al., there were no different responses of FMD, basal endothelial nitric oxide (NO) production and stimulated release of tissue plasminogen activator between 16 migraine patients and 16 non-migraine controls [23]. Hamed et al. measured FMD in 63 patients with headache (14 patients with MA, 24 patients with MO, 6 patients with transformed migraine and 19 patients with tension headache) and 35 healthy subjects. Brachial artery FMD% was normal in MA and MO patients. Abnormal FMD was found in patients with transformed migraine [24].

Rodríguez-Osorio et al. examined FMD of the dominant brachial artery in 47 patients with episodic migraine and 23 control subjects. No significant changes of FMD were found during the interictal period or headache of migraine patients [25].

Forearm blood flow changes during acetylcholine (ACh) infusion in migraineurs: In 12 MO patients and 12 healthy controls, endothelial and vascular smooth muscle cell (VSMC) components of vascular reactivity were examined during the infusion of acetylcholine (ACh) into the brachial artery by plethysmography. Forearm production of NO and cyclic guanosine monophosphate (cGMP) was also quantified. In migraine patients, vasodilating effects of ACh were markedly reduced. During ACh infusion, NO release from the endothelium was similar between patients and controls. In contrast, a marked release of cGMP from VSMCs was found in controls, but not in migraine patients. Migraineurs had the distinct vascular dysfunction [26].

Arterial elasticity in migraineurs: Most of PWV and Alx studies assessing the arterial elasticity and distention suggested abnormal findings in the large- or medium-sized artery of migraineurs [19,21,27-31]. We explained the following main literature of normal or increased arterial stiffness on PWV and Alx in migraineurs.

PWV in migraineurs: Following three studies addressed PWV in migraineurs [27-29]. Two studies showed abnormal PWV in migraineurs [27,28]. Only one study reported normal PWV in MA and MO patients [29]. The possibility is suspected that normal studies of PWV may be unpublished.

Increased PWV in migraineurs: Schillaci et al. measured cPWV in 60 migraine patients and 60 healthy subjects matched by age, sex and blood pressure. All patients and controls had
no major CVD risk factors. cfPWV was significantly higher in migrainers compared to control subjects. That was in MA patients than that in MO patients. Migraine had increased pressure wave reflection [27].

Another study of Ikeda et al. exhibited baPWV, using an oscillometric technique, in 111 migrainers (22 MA and 89 MO patients) and 110 controls. All participants had no CVD risk factors. baPWV was increased significantly in female and male migrainers compared to controls. However, migraine subtypes, duration, severity and attack frequency were not associated with baPWV. The pathogenesis of higher baPWV could reflect the distinct vascular response rather than atherosclerosis [28].

Normal PWV in migrainers: Intima-media thickness (IMT) of the carotid artery and PWV were assessed in 360 migrainers (151 MA and 209 MO patients) and 617 control subjects without migraine or severe headache. There were no significant differences of IMT and PWV between MA, MO patients and controls [29].

Increased Aix in migrainers: Following five studies showed increased Aix in migrainers [19,21,27,30,31]. Aix was measured in the radial artery [30], the aorta [19,27] and the finger artery [30,31]. We mentioned previous studies of increased Aix in chronological order. Aix of the radial artery was measured in two groups of migrainers. Aix was increased significantly in migrainers. Migraine in the elderly could be a clinical manifestation of enhanced arterial stiffness [30]. Vanmol kot et al. analyzed arterial stiffness in 50 patients with recent onset of migraine patients and 50 age- and sex-matched control subjects. Aortic Aix was increased in migraine patients [19].

Schillaci et al. examined cFPWV and aortic Aix by applanation tonometry in 60 migrainers and 60 healthy subjects matched by age, sex and blood pressure. All participants had no major CVD risk factors. Aortic Aix was significantly higher in migrainers compared to control subjects. Migraine is independently associated with increased aortic stiffness [27].

Liman et al. studied carotid IMT, peripheral arterial tonometry of the brachial artery and fingertip Aix in 29 MA women without comorbidities and 30 healthy women. There were no differences of peripheral arterial tonometry ratio and left carotid intima-media thickness between MA patients and control subjects. MA women had higher heart-rate-averaged and heart-rate-adjusted Aix than those of healthy controls. Peripheral endothelial function was normal in MA women whereas arterial stiffness was increased [31].

In the study by Jiménez Caballero et al., finger Aix was measured in 21 patients with chronic migraine and 21 healthy controls. Aix was increased in migrainers compared to healthy controls. Chronic migrainers have increased arterial stiffness in the peripheral artery [21].

Ankle-brachial index (ABI) in migrainers: ABI has been defined as the ratio of the systolic blood pressure in the posterior tibial and the brachial artery. This test is used widely as a surrogate of peripheral obstructive arterial disorders. Three previous studies of ABI were reported in migrainers. Two studies concluded normal ABI in migrainers [28,29]. Only one study reported lower ABI in migraine patients compared to control subjects [32].

Lower ABI in migrainers: ABI, using digital sphygmomanometry, was performed in 50 migrainers and 38 controls. The mean (SD) of ABI was 0.94 (0.11) in migrainers and 0.99 (0.09) in controls. ABI values were decreased significantly in migrainers [32].

Normal ABI in migrainers: ABI, using an oscillometric technique of arterial tonometry, was performed in 111 migrainers (81 women and 30 men) and 110 control subjects who had no CVD risk factors. ABI did not differ statistically between migrainers and controls. Migraine subtypes, duration, attack frequency, and Headache Impact Test-6 score were not associated with ABI [28].

Recent study by Stam et al. showed ABI in 360 migrainers (151 MA and 209 MO patients) and 617 control subjects without migraine or severe headache. ABI did differ statistically between MA, MO patients and controls [29].

Brain MRA in migrainers: Brain MRA is applied widely for a non-invasive examination of the cerebral arteries. Two morphological studies of the circle of Willis (CW) were reported previously in migrainers [33,34].

Morphology of posterior CW in migrainers: Bugnicourt et al. explored CW shapes on brain MRA in 47 migraine patients (24 MA and 23 MO patients) and 77 control patients with other neurologic disorders. The posterior CW was defined as the complete type when both posterior communicating arteries and the P1 segments of the posterior cerebral artery were visualized on maximum intensity projection (MIP) imaging. Incomplete type of the posterior CW showed when one or both of these vessels were absent. Incomplete posterior CW was significantly more common in migrainers than in controls. There were no significant differences between MA and MO patients. On multivariate analysis, incomplete posterior CW was an independent factor associated with migraine [33].

Another study of Ikeda et al. examined brain MRA in 73 migrainers (31 MA and 42 MO patients) and 100 age-matched control subjects. MIP and source imaging of MRA were reviewed. Complete and incomplete posterior CW was classified according to a previous study [33]. As compared with controls, migrainers and MA patients significantly decreased the frequency of complete posterior CW. No significant changes of posterior CW were found between MO patients and controls. Posterior CW patterns were not correlated with other clinical aspects of migrainers, including age, sex, onset age, and duration of migraine [34].

CONCLUSIONS

In the past decade, many studies have suggested that the noninvasive examination of endothelial function and arterial elasticity may provide important information for developing CVD. Otherwise, whether the clinical implications of endothelial dysfunction and arterial changes remains unclear in migrainers. The current consensus indicates that the vascular alternation could play a role in the risk for developing CVD and stroke in a part of migrainers, especially MA patients. Further longitudinal vascular studies were needed to elucidate whether endothelial
dysfunction and increased arterial stiffness persist from young-aged to elderly migraineurs.

REFERENCES