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Mini-Review

Carotid Stiffness: A Novel Cerebrovascular Disease Risk Factor

Thomas T. van Sloten Coen D.A. Stehouwer

Department of Internal Medicine and the Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, The Netherlands

Key Words
Carotid stiffness · Cerebrovascular disease

Abstract
Carotid stiffening is considered an important element in the pathogenesis of cerebrovascular diseases. These include stroke as well as vascular dementia and depression. However, results of individual studies evaluating the association between carotid stiffening and incident stroke have been inconsistent. Therefore, we have conducted a systematic review and meta-analysis, showing that carotid stiffening is associated with incident stroke independently of cardiovascular risk factors and aortic stiffness. In addition, carotid stiffening improved stroke risk prediction beyond the Framingham stroke risk factors and aortic stiffness. Other studies have shown that carotid stiffening is associated with a higher incidence of vascular dementia and depressive symptoms. This suggests that carotid stiffness is a potential separate target for prevention strategies of cerebrovascular disease.

Cerebrovascular disease is one of the leading causes of disability and mortality worldwide [1–3]. The global burden of cerebrovascular diseases, including stroke as well as vascular dementia and depression, has greatly increased in the last decades and will continue to increase in the coming years [3]. Therefore, effective prevention strategies need to be developed, which require a better understanding of cerebrovascular disease risk factors.

Stiffening of the carotid artery (or of other elastic arteries for which the carotid artery may serve as a proxy) may lead to cerebrovascular disease via multiple mechanisms (fig. 1). Increased stiffness of the carotid artery leads to a higher pulsatile pressure and flow load on the brain [4–6]. This increased load can penetrate distally into the cerebral microcirculation and may directly cause cerebral ischemia and hemorrhage. The brain may be particularly

C.D.A. Stehouwer, MD, PhD
Department of Internal Medicine, Maastricht University Medical Centre
Prof. Debyelaan 25
NL–6229 HX Maastricht (The Netherlands)
E-Mail cda.stehouwer@mumc.nl

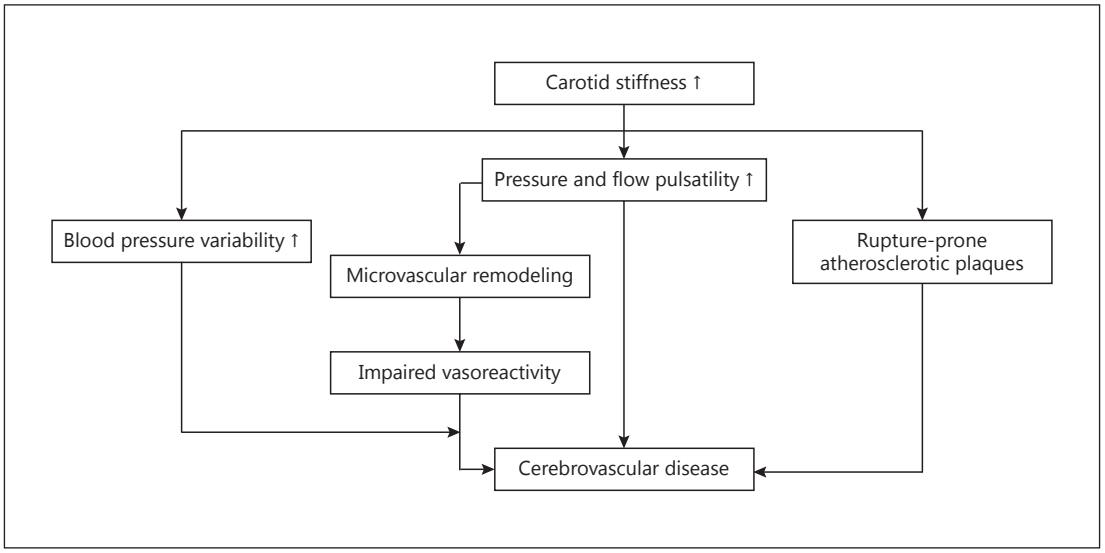

Fig. 1. Potential pathways by which arterial stiffening can lead to cerebrovascular disease.

prone to the detrimental effects of an increased load, because its microcirculation is characterized by low impedance, allowing the pulsatile load to penetrate deeply into its microvascular bed [4, 5]. Also, the increased pulsatile load may induce a hypertrophic remodeling response and rarefaction of small cerebral arteries, which initially serves to limit the penetration of the pulsatile load into the microcirculatory system by raising vascular resistance [6]. However, this protective response may ultimately become unfavorable, leading to impaired vasoreactivity, hypoperfusion and chronic ischemia. In addition, increased stiffness of elastic arteries may cause excessive blood pressure variability [7, 8], which may further sensitize high-flow organs to the harmful effects of impaired microvascular vasoreactivity [4]. Finally, carotid artery stiffening may lead to cerebrovascular disease through local development of rupture-prone atherosclerotic plaques [6, 9].

We have performed a systematic review and an aggregate and individual participant data meta-analysis [10] to evaluate the association between carotid stiffening and incident stroke. The aggregate data meta-analysis, which included ten studies (n = 22,472), showed that greater carotid stiffness was associated with a higher stroke incidence. In addition, carotid stiffening was associated with incident total cardiovascular events and cardiovascular and all-cause mortality, but not with coronary heart disease events. An additional individual participant data meta-analysis, which included four studies (n = 4,540), showed that additional adjustment for aortic stiffness, as measured by carotid-femoral pulse wave velocity (cfPWV), did not materially change these associations (table 1). Furthermore, carotid stiffening improved stroke risk prediction beyond the Framingham stroke risk factors and cfPWV, as indicated by a statistically significant integrated discrimination improvement and continuous net reclassification improvement (table 1).

This study thereby identifies carotid stiffening as a potential separate target for stroke risk-lowering therapy. Cardiovascular disease risk factors have different impacts on stiffening of elastic versus muscular arteries [11, 12]. This may be attributed to the marked differences in the architecture of these arteries and suggests that stiffening of elastic arteries may be specifically targeted. Currently, however, no effective clinical therapy is available that specifically targets stiffening of elastic arteries.

Table 1. Results of individual participant data meta-analysis [10]

Models	Carotid DC (per 1 lower SD) as the determinant and incident stroke as the outcome[1]
Cox regression analysis	Hazard ratio (95% confidence interval)
Model 1[2]	1.24 (1.05; 1.47)
Model 1[2] + cfPWV	1.24 (1.05; 1.46)
Risk improvement analysis[3]	Effect estimate (95% confidence interval)
IDI, % point	0.4 (0.1; 0.6)
Continuous NRI, %	18.6 (5.8; 31.3)

Association between carotid stiffness and incident stroke: additional adjustments for cfPWV and analysis of risk improvement. The model was extended by the carotid distensibility coefficient (DC). SD = Standard deviation; IDI = integrated discrimination improvement; NRI = net reclassification index.

[1] Number of participants for this analysis: n = 4,075, with 351 events and 47,881 person-years of follow-up.

[2] Model 1: results adjusted for age, sex, mean arterial pressure, heart rate, body mass index, smoking habits, diabetes, triglycerides, total/high-density lipoprotein cholesterol ratio, prior cardiovascular disease, and the use of lipid-modifying and antihypertensive medication.

[3] The baseline model for risk improvement analysis included the Framingham stroke risk score factors and cfPWV.

In addition, the study provides proof of principle that carotid stiffening can have additional value as a risk predictor of stroke. However, the improvement in stroke risk prediction by carotid stiffening was modest. Furthermore, the study included high-risk populations (i.e. older individuals and/or individuals with diabetes or chronic kidney disease). In these populations, such a modest improvement may not be clinically relevant [13]. Nevertheless, the study provides a framework for investigating whether assessment of carotid stiffness can improve stroke risk prediction in younger individuals and in those at intermediate risk for stroke, in whom improvement in risk prediction may be of greater importance [14].

Recent studies have suggested that carotid stiffening may also lead to brain diseases other than stroke, including dementia and late-life depression, and that these associations are mediated by cerebrovascular damage. Cerebrovascular damage plays an important role in the pathogenesis of cognitive impairment, including dementia [15]. In addition, it has been suggested [16–18] that cerebral microvascular damage leads to depression via disruption of deep and frontal brain structures or their connecting pathways involved in mood regulation, in particular in older individuals (vascular depression hypothesis). Systematic reviews and meta-analyses [19, 20] have shown an association between arterial stiffening (including carotid stiffening) and cognitive impairment. In addition, The Rotterdam Study [21] has shown an association between increased carotid stiffness and a higher incidence of depressive symptoms. Furthermore, the AGES-Reykjavik Study [22, 23] showed that the associations of arterial stiffening with cognitive impairment and depressive symptoms are in part mediated by cerebral small vessel disease.

In conclusion, greater carotid stiffness is associated with a higher incidence of stroke, and carotid stiffening modestly improved risk prediction of stroke beyond the Framingham stroke risk score factors and cfPWV. Furthermore, carotid stiffening may lead to brain diseases other than stroke, including vascular dementia and depression, and these associations may be mediated by cerebrovascular damage. This identifies carotid stiffening as a potential separate target for prevention strategies of cerebrovascular disease.

Disclosure Statement

The authors declare no conflicts of interest.

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