Artery Research (2017) 19, 18–23

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

Review

Vascular dysfunction: At the heart of cardiovascular disease, cognitive impairment and depressive symptoms☆

T.T. van Sloten*

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

Received 6 November 2016; received in revised form 12 April 2017; accepted 7 May 2017

KEYWORDS
Arterial stiffness;
Endothelial dysfunction;
Cerebral small vessel disease;
Dementia;
Depression

Abstract Vascular dysfunction may be an important pathway through which ageing and other factors, such as diabetes and obesity, can cause diseases of the heart and brain. Vascular dysfunction includes dysfunction of large arteries (due to arterial stiffness), the microcirculation (microvascular dysfunction) and endothelium (endothelial dysfunction). We have investigated, in a series of epidemiological studies, the role of vascular dysfunction in the pathogenesis of cardiovascular disease, dementia and depression. Data were used of The Hoorn Study, The AGES-Reykjavik Study, The Maastricht Study and The SUVIMAX2 Study. In addition, we did two systematic reviews and an individual participant data meta-analysis.

Contents

Stiffening of elastic and muscular segments: distinct pathways in the pathogenesis of cardiovascular events . . . 19
Arterial stiffening and endothelial dysfunction: causes of cerebral microvascular damage, cognitive impairment and depressive symptoms . . . 20
Arterial stiffening does not lead to generalized microvascular dysfunction . . . 20
Endothelial dysfunction and type 2 diabetes synergistically increase cardiovascular risk . . . 21
Pathophysiological model . . . 21

☆ Review linked to Career Development Lecture, Artery Meeting, Copenhagen, 2016.

* Maastricht University Medical Centre, Department of Medicine, Prof. Debyelaan 25, 6229HX Maastricht, The Netherlands. Fax: +31 433875006.
E-mail address: t.vansloten@maastrichtuniveristy.nl.

http://dx.doi.org/10.1016/j.artres.2017.05.002

Future perspectives 21
Conflict of interest 22
References 22

We found that stiffening of the carotid artery is independently associated with incident stroke, but not with coronary heart disease. Furthermore, carotid stiffness improved stroke risk prediction beyond Framingham and cfPWV. In addition, femoral artery stiffening was independently associated with incident cardiovascular disease.

Brain MRI studies showed that cerebral small vessel disease is associated with cognitive decline and incident depressive symptoms. In addition, arterial stiffening was associated with cognitive impairment and depressive symptoms, and this association was mediated by cerebral small vessel disease. We also found that endothelial dysfunction is associated with more depressive symptoms. Finally, we showed the presence of interaction (synergy) with regard to cardiovascular risk, between endothelial dysfunction and type 2 diabetes.

From a clinical point of view, these associations are important as they suggest that efforts at favourably influencing vascular dysfunction can have significant public health implications via prevention of cardiovascular disease, dementia and depression.

Life expectancy has dramatically increased and will continue to do so in the next decades.[1] Ageing is associated with a greatly increased risk of vascular-related diseases of the heart and brain, including coronary heart disease, heart failure, stroke and (vascular) dementia and depression. In recent years, emerging evidence indicates that dysfunction of various elements of the vascular system plays an important role in the pathogenesis of these diseases.[2,3] Vascular dysfunction includes dysfunction of large arteries (due to arterial stiffening), the microcirculation (microvascular dysfunction) and endothelium (endothelial dysfunction). Indeed, recent statements of the European Society of Hypertension/European Society of Cardiology[4] and the American Heart Association/American Stroke Association[5] have indicated arterial stiffness and endothelial dysfunction as important, potentially modifiable risk factors for cardiovascular disease and cognitive impairment. However, the exact role of arterial stiffness and microvascular and endothelial dysfunction in the pathogenesis of these diseases is incompletely understood, and their clinical utility remains controversial. Therefore, we have investigated, in a series of epidemiological studies, the role of arterial stiffness and microvascular and endothelial dysfunction in the pathogenesis of cardiovascular disease, cognitive impairment and depressive symptoms. This paper discusses the key findings of our recent work and their potential clinical implications.

Stiffening of elastic and muscular segments: distinct pathways in the pathogenesis of cardiovascular events

There are substantial differences in properties between elastic and muscular segments, and it has been suggested[6] that stiffening of these segments are differentially associated with cardiovascular events. Stiffening of elastic segments (e.g. the carotid artery and ascending aorta) may be more strongly associated with stroke than coronary heart disease, because stiffening of these segments leads to a high pulsatile pressure and flow load on the brain.[7] In addition, stiffening of the carotid artery may lead to stroke through local development of rupture-prone atherosclerotic plaques.[8] In contrast, stiffening of muscular segments (e.g. the femoral artery and descending aorta) may be more strongly associated with coronary heart disease events than stroke, because muscular and coronary arteries show similar arterial wall characteristics (i.e. presence of abundant smooth muscle cells and a high collagen/elastin ratio[9]), and, therefore, stiffening of muscular segments may serve as a proxy for stiffening of the coronary vasculature. We used data of The Hoorn Study[10] on local distensibility measurements of the carotid and femoral arteries to investigate elastic and muscular artery stiffness.[7] In line with the above hypothesis, the findings indicated that stiffening of the carotid and femoral arteries are associated with a higher cardiovascular event incidence and greater all-cause mortality risk, independently of each other, and independently of carotid-femoral pulse wave velocity (cfPWV). We further elaborated upon these findings and performed a systematic review and an aggregate data and an individual participant data meta-analysis[11] on the association between carotid stiffness and incident cardiovascular events. The results showed that carotid stiffening is associated with a higher stroke incidence, but not with coronary heart disease events. The association between carotid stiffness and incident stroke was independent of cardiovascular risk factors and independent of cfPWV. In addition, estimation of carotid stiffness modestly improved stroke risk prediction beyond Framingham stroke risk score factors and cfPWV. From a clinical point of view, these observations are important, as they identify carotid and femoral stiffness as potential separate targets for stroke and coronary heart disease risk lowering therapy. In addition, the findings provide proof of principle that carotid stiffness can have additional value as a risk predictor of stroke beyond the Framingham stroke risk score factors and cfPWV.