Causes and consequences of microvascular dysfunction

Valorisation addendum

The goal of scientific research is to establish new facts and to reach new conclusions, but without any impact to society, these new conclusions would have little consequences. The goal of this chapter is to discuss the impact on society of the conclusions reached in this thesis, and to discuss any recommendations for further research on this topic in order to maximize this impact.

Relevance of this research

In the Netherlands and most other parts of the world, life expectancy has been increasing for the last couple of decades and will continue to do so for some more decades to come. With the increasing age of the population, the amount of individuals with a high burden of cardiovascular risk factors increases. More importantly, so does the number of individuals with age-related brain diseases such as dementia, late-life depression and stroke. The findings in this thesis suggest that deterioration of the microvasculature, i.e. the vascular meshwork comprised of arterioles, capillaries and venules, is an important contributor to the development of these age-related brain diseases. In addition, this thesis suggests that microvascular deterioration, also called microvascular dysfunction, mediates the association between cardiovascular risk factors and age-related brain diseases.

The conclusions in this thesis provide an important contribution to our current understanding of the pathophysiology of age-related brain diseases and indicate that prevention and/or treatment of microvascular dysfunction may be an important clinical goal. In practice, to prevent or slow down progression of age-related brain diseases in individuals with microvascular dysfunction, early and adequate cardiometabolic health must be pursued. Moreover, interventions aiming to favourably influence microvascular function on top of cardiometabolic management may provide additional prevention of age-related brain diseases.

Future research

Before studies on prevention of and intervention for microvascular dysfunction can be conducted, further longitudinal observational studies are needed to confirm the causal relationship between cardiovascular risk factors, microvascular dysfunction, and age-related brain diseases. Although the results in this thesis are consistent across all chapters, only chapter 2 and chapter 3 describe longitudinal relationships from which temporal associations, and thus causality, may be implied. Furthermore, in the present thesis, microvascular dysfunction was defined as a higher composite score of several measures of microvascular dysfunction, and sometimes specifically by measures of cerebral small vessel disease, instead of clinically relevant microvascular disease. There is currently no scale to define clinically relevant microvascular dysfunction based on the measures of microvascular dysfunction used in this thesis. Future studies are therefore needed to evaluate at what point microvascular dysfunction becomes clinically relevant, and whether the observed associations with microvascular dysfunction and age-related brain diseases are also present at this point. This thesis already demonstrated that the combination of two cerebral small vessel disease features is most strongly associated with incident stroke. This suggests that scales that incorporate the effect of multiple measures of microvascular

function are most suitable to assess microvascular dysfunction, and most likely to enable improved risk prediction of clinical outcomes beyond established risk factors.

In addition to observational studies, randomized controlled trials are needed to evaluate the possible effectiveness of interventions for microvascular dysfunction. Currently, evidence for improved outcome with treatment programs aimed at strict cardiovascular risk management in patients with microvascular dysfunction is lacking. It has been suggested however, that statins, ACE inhibitors and aspirin improve microvascular function by mechanisms beyond their respective lipid-lowering, blood pressure-lowering and anticoagulant effects; the so-called pleiotropic effect.

Clinical recommendations

As stated above, there are currently no comprehensive guidelines available for the diagnosis and treatment of microvascular disease. In 2013, the STRIVE neuroimaging standards to aid in the standardized assessment of microvascular disease in the brain were published. However, it is not advisable for a clinician to actively screen for microvascular dysfunction using neuroimaging or other techniques, given the current lack of guidelines for intervention. However, features of microvascular dysfunction are often found as incidental findings on scans with other primary indications. A clinician should, upon diagnosing a patient with microvascular dysfunction, be prompted to perform adequate cardiovascular risk assessment. The risk factors that are associated to macrovascular disease appear to be similarly associated with microvascular dysfunction; e.g. smoking, type 2 diabetes, obesity, hypertension and hyperlipidaemia. As such, treatment aimed at cardiovascular risk factor management, including lifestyle counselling regarding smoking cessation, nutrition and physical activity is warranted.

Conclusion

The findings in this thesis suggest that identification and treatment of microvascular dysfunction can be helpful in prevention of age-related brain disease.