Microvascular dysfunction, physical activity, and cardiometabolic diseases

Valorisation addendum

Social and economic relevance

Ideally, any theoretical and technological innovation in medical research can be applied to practice. However, Rome was not built in a day; it was built due to unremitting efforts of several generations. When M. Malpighi and A. van Leeuwenhoek first observed the blood flow through capillaries under the microscope, they might not have realized that a new chapter in the knowledge of circulation and its (patho)physiological functions embarked. Moreover, the finding has driven the industry which developed a variety of techniques to quantitatively assess microvascular function. This is also the case for assessments of physical behavior. As we described in the previous chapters, we have gained more knowledge by use of these assessments in the population-based cohort. Although this dissertation only investigates microvascular (dys)function and physical (in)activity as determinants of cardiometabolic diseases, further investigations may focus on their values of prevention and treatment based on our findings. If these assessments are proven to have higher values of prevention and treatment, they are expected to reduce premature death, disability, and medical expenses due to cardiometabolic diseases.

Target group

Our study population included middle- to older-aged population. Nevertheless, our findings may be generalized to a broader population, even to young adults. According to our results, better microvascular function and physical activity at baseline reduced participants' risk of cardiovascular diseases at any given time. Previous meta-analyses have shown that microvascular dysfunction is associated with a higher risk of type 2 diabetes which may occur after 10 years [1,2]. These results support a concept that the risk of cardiometabolic diseases may begin to increase at a younger age, and preventive awareness and measures should be taken earlier.

Innovation

The application of innovative technologies in this dissertation have enhanced the reliability of our findings and confirmed the feasibility of their use in a large population. The use of multiple microvascular measurements enabled us to assess microvascular function across vascular beds (i.e., arterioles, venules, and capillaries) and territories and their similarity and difference

in response to various (patho)physiological conditions. No previous studies have applied such systems physiology approach. Regarding the measurement of physical behaviors, we also included multiple parameters to investigate the effect of volume and pattern of physical behaviors on the risk of cardiovascular disease. In addition, we used thigh-worn accelerometers, which is more accurate than hip-worn accelerometers and self-reported physical activity questionnaires to assess physical activity.

The extensive phenotyping in The Maastricht Study has allowed us to investigate independent associations adjusted for many potential confounders. Additionally, it allowed further exploration of underlying mechanisms. For instance, it has been proposed that diabetes-associated retinal venular dilation is related to inflammation [3,4]. However, additional adjustment for inflammation did not change the association between (pre)diabetes and retinal venular diameters in our study (**Chapter 3**), suggesting that inflammation may not explain the retinal venular dilation.

Implementation

Microvascular measurements for screening

If microvascular dysfunction can predict the risk of cardiometabolic diseases with high sensitivity, the measurements may be used for screening. Among the specific measurements, the fundus photography is common in hospitals and time-saving. The Atherosclerosis Risk in Communities (ARIC) Study reported that assessing retinal microvascular diameters in addition to the Pooled Cohort Equations would reclassify 21% of low-risk women as intermediate risk [5]. However, determining cut-off values is necessary for screening but difficult. We and others have found that (pre)diabetes is associated with wider retinal arterioles (**Chapter 3**), whereas narrower retinal arterioles are associated with a higher risk of cardiovascular diseases. This may suggest different pathophysiological mechanisms as well as a bidirectional change in retinal arteriolar diameters with the progression of disease. In addition, we should take into account the strong confounding effects of age, sex, blood pressure and BMI (or waist circumference).

Microvascular function as a target of treatment

Current evidence supports that microvascular dysfunction may play a role in cardiometabolic diseases (**Chapter 3 and 5**) [1,2,5]. Therefore, interventions on microvascular function may be promising for the treatment. Some medications on the market have already shown efficacy in improving microvascular function. For instance, calcium dobesilate, a vasoprotective that reduces capillary permeability, can effectively alleviate diabetic retinopathy and nephropathy [6,7]. Some traditional Chinese medicine, antihypertensive and antihyperglycemia agents, and lifestyle interventions can also improve microvascular function [8-10], but whether the improvement can retard the development of cardiometabolic diseases needs further investigation. Another important question is when the intervention should be implemented. As microvascular dysfunction can occur long before the diagnosis of diabetes and cardiovascular diseases, early intervention may be taken for prevention. Of note, clinicians need to assess other profiles of patients before and after applying the medication, as most of the current medications are non-specific to microvasculatures.

Physical activity for prevention and treatment of cardiometabolic diseases

Lifestyle interventions often serve as primary prevention strategies for cardiometabolic diseases, with the advantages of less expenses and side effects. A meta-analysis showed that diet and physical activity interventions for adults without known cardiometabolic risk factors benefit cardiovascular health in 6-12 months of follow-up with a dose-response relationship [11]. In addition, adults at high risk may benefit more from these interventions [12]. With regard to long-term benefits, a recent meta-analysis showed that more daily step counts are associated with a lower risk of all-cause mortality, and cardiovascular morbidity and mortality in adults [13]. Another meta-analysis revealed that more self-reported sedentary behavior may increase the risk of all-cause and cardiovascular mortality and incident type 2 diabetes, independently of physical activity time [14]. However, we found that accelerometer-measured sedentary time is not independently associated with incident non-fatal cardiovascular disease (**Chapter 6**). The results are similar in children and adolescents; more moderate-to-vigorous-intensity physical activity (MVPA) is associated with better cardiometabolic risk factors, whereas sedentary time is not associated with cardiometabolic risk factors independently of MVPA [15]. In addition, physical activity can improve physical fitness and reduce disability in patients with stroke [16], and reduce all-cause hospital admissions and cardiovascular mortality in patients with coronary heart disease [17].

Taken together, physical activity can be an effective intervention for the prevention and treatment of cardiometabolic diseases, whereas the evidence showing the cardiometabolic benefits of decreased sedentary time remains insufficient. Advocacy via media and increasing public fitness equipment may facilitate physical activity of people. For individuals, the type and intensity of physical activity should be selected with consciousness of safety and long-term compliance.

Conclusion

In summary, identification of potential risk factors and treatments is expected to lower the burden of cardiometabolic diseases on the patients and society. This dissertation provides robust evidence which shows microvascular (dys)function and physical (in)activity as determinants of cardiometabolic diseases and promising targets for the prevention and treatment. However, further investigations are needed to evaluate the rationality and feasibility of their use in the clinical practice.

Reference

1. Muris DM, Houben AJ, Schram MT, Stehouwer CD. Microvascular dysfunction is associated with a higher incidence of type 2 diabetes mellitus: a systematic review and meta-analysis. Arterioscler Thromb Vasc Biol. 2012;32(120):3082-3094.
2. Sabanayagam C, Lye WK, Klein R, Klein BE, Cotch MF, Wang JJ, et al. Retinal microvascular calibre and risk of diabetes mellitus: a systematic review and participant-level meta-analysis. Diabetologia. 2015;58:2476-2485.
3. Nguyen TT, Wang JJ, Sharrett AR, Islam FA, Klein R, Klein BE, et al. Relationship of retinal vascular caliber with diabetes and retinopathy: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care. 2008;31(3):544-549.
4. Klein R, Klein BE, Knudtson MD, Wong TY, Tsai MY. Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. Arch Ophthalmol. 2006;124:87-94.
5. Seidelmann SB, Claggett B, Bravo PE, Gupta A, Farhad H, Klein BE, et al. Retinal vessel calibers in predicting long-term cardiovascular outcomes: the atherosclerosis risk in communities study. Circulation. 2016;134(18):1328-1338.
6. Zhang X, Liu W, Wu S, Jin J, Li W, Wang N. Calcium dobesilate for diabetic retinopathy: a systematic review and meta-analysis. Sci China Life Sci. 2015;58(1):101-107.
7. Haller H, Ji L, Stahl K, Bertram A, Menne J. Molecular Mechanisms and treatment strategies in diabetic nephropathy: new avenues for calcium dobesilate—free radical scavenger and growth factor inhibition. Biomed Res Int. 2017;2017:1909258.
8. Stehouwer CD. Microvascular dysfunction and hyperglycemia: a vicious cycle with widespread consequences. Diabetes. 2018;67(9):1729-1741.
9. Climie RE, van Sloten TT, Bruno RM, Taddei S, Empana JP, Stehouwer CD, et al. Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension. Hypertension. 2018;73(6):1138-1149.
10. Han B, Zhang X, Zhang Q, Zhao G, Wei J, Ma S, et al. Protective effects of salvianolate on microvascular flow in a porcine model of myocardial ischaemia and reperfusion. Arch Cardiovasc Dis;104(5):313-324.
11. Patnode CD, Evans CV, Senger CA, Redmond N, Lin JS. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults without known cardiovascular disease risk factors: updated evidence report and systematic review for the US Preventive Services Task Force. Jama. 2017;318(2):175-193.
12. Zabaleta-del-Olmo E, Bolibar B, García-Ortíz L, Garcia-Campayo J, Llobera J, Bellón JÁ, Ramos R. Building interventions in primary health care for long-term effectiveness in health promotion and disease prevention. A focus on complex and multi-risk interventions. Prev Med. 2015;76 Suppl:S1-S4.
13. Hall KS, Hyde ET, Bassett DR, Carlson SA, Carnethon MR, Ekelund U, et al. Systematic review of the prospective association of daily step counts with risk of mortality, cardiovascular disease, and dysglycemia. IInt J Behav Nutr Phys Act. 2020;17(1):78.
14. Patterson R, McNamara E, Tainio M, de Sá TH, Smith AD, Sharp SJ, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol. 2018;33(9):811-829.
15. Ekelund U, Luan JA, Sherar LB, Esliger DW, Griew P, Cooper A, International Children's Accelerometry Database (ICAD) Collaborators. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. Jama. 2012;307(7):704-712.
16. Saunders DH, Sanderson M, Hayes S, Johnson L, Kramer S, Carter DD, et al. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2020;3(3):CD003316.
17. Chair SY, Zou H, Cao X. Effects of Exercise Therapy for Adults With Coronary Heart Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials [published online ahead of print, 2020 Jul 3]. J Cardiovasc Nurs. 2020;10.1097/JCN.0000000000000713.