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Table 1 Figure 1

Association between estimated pulse wave velocity and the risk of stroke in middle-aged men

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ABSTRACT

Aims and methods. We sought to examine the association between estimated pulse wave velocity (ePWV), a proxy of carotid-femoral pulse wave velocity, and stroke and its subtypes (ischemic and hemorrhagic) in a prospective cohort of 2,666 men (aged mean 53.1, range 42-61 years) enrolled in the Kuopio Ischemic Heart Disease cohort study. **Results**. During a median 28-year follow-up, 471 incident stroke (397 ischemic and 94 hemorrhagic) events occurred. After adjusting for several established and emerging risk factors including age and pulse pressure, com paring the top versus bottom quartiles of ePWV, there was an increased risk of stroke (hazard rati o [HR] 2.37, 95% Confidence Interval [CI]: 1.57-3.58), ischemic stroke (HR 2.23, 95% CI, 1.42-3.50), and hemorrhagic stroke (HR 3.57, 95% CI, 1.45-8.76). **Conclusion.** These findings demonstrate that ePWV is independently associated with the risk of stroke in middle-aged men.

Keywords: vascular stiffness; pulse wave velocity; cerebrovascular; blood pressure

Introduction

Stroke is considered the second leading cause of mortality and disability worldwide.(1) In the United States, approximately 795,000 individuals have a stroke each year claiming over 140,000 lives and costing an estimated $34 billion in health care.(1) By the year 2030, it is estimated that 4% of US adults will have had a stroke. Blood pressure (BP) is a major risk factor for stroke. With advancing age, there are increases in systolic BP with slight decreases in diastolic BP resulting in a widening of pulse pressure (PP). Increases in PP are attributable to large artery stiffening and are predictive of adverse cerebrovascular outcomes, particularly in middle-aged and older adults.(2)

Recently, another BP-derived measure of large artery stiffening has emerged. Estimated pulse wave velocity (ePWV), a proxy of carotid-femoral pulse wave velocity (cfPWV) which is the gold-standard measure of aortic stiffness, has been shown to be associated with cardiovascular outcomes and all-cause mortality in hypertensive adults (3) and in the general population.(4-6) Given that cfPWV is independently associated with risk of incident stroke,(7, 8) we sought to examine the association between ePWV and stroke in the general population. We hypothesized that ePWV would be associated with stroke risk as well as its subtypes (ischemic and hemorrhagic).

Methods

This prospective study was based on a sample of 2,666 middle-aged men (aged mean SD 53.1±5.1, range 42-61 years) from the Kuopio Ischemic Heart Disease (KIHD) cohort study. The KIHD study is on ongoing, prospective population-based cohort study. Baseline examinations were conducted between 1984-1989 with follow-up examinations conducted 4-years later (1991-1993), 11 years later (1998-2001) and 18-years later (2005-2008).(9) The overarching purpose of this study is to investigate CVD risk factors, atherosclerosis and related clinical outcomes in middle-

aged men from eastern Finland. Baseline measures included a detailed medical history, sociodemographic information (education, annual income, marital status), questions on biobehavioral factors and lifestyle (smoking, alcohol, physical activity), measurement of anthropometrics (height and weight for calculation of body mass index), fasting venous blood samples for the derivation of circulating lipids and fasting glucose, and measurement of blood pressure.(9) The study protocol was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland, in line with the Helsinki Declaration, and each participant provided written informed consent.

ePWV was calculated from an equation based on age and mean blood pressure (MBP)(10): $ePWV = 9.587 - 0.402 \times age + 4.560 \times 10^{-3} \times age^2 - 2.621 \times 10^{-5} \times age^2 \times MBP + 3.176 \times 10^{-3} \times age \times MBP - 1.832 \times 10^{-2} \times MBP$. MBP was calculated as DBP + 0.4 * PP with PP being taken as SBP-DBP. This equation is derived from the Reference Values for Arterial Stiffness Collaboration, which consisted of pooling cfPWV measures from 16,867 participants across 13 different centers spanning eight European countries.(11) The equation recognizes that age and MBP are the most prominent predictors of cfPWV and considers nonlinearities and interactions between age and MBP in the derivation of ePWV.(11) Levels of ePWV were categorized according to quartiles (<8.5 [the lowest], 8.5-9.2, 9.2-10.0, and >10.0 m/s [the highest]).

Incident strokes were ascertained through the FINMONICA (Finnish Monitoring Trends and Determinants in Cardiovascular Diseases) stroke registry between 1984 and 1992 (12, 13) and by computerized linkage to the Finnish national hospital discharge registry between 1993 and 2017. Each patient has a unique personal identifier used in the registers and there were no losses to follow-up. Diagnostic information was collected from hospitals and classified by a neurologist with diagnostic criteria identical to the FINMONICA criteria.(12, 13) Stroke was operationally

defined as sudden onset of clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours with no apparent cause other than a vascular origin.(12, 13) More details about the diagnostic classification of strokes have been described previously.(14) Briefly, stroke was classified as (1) an ischemic stroke (ICD-9 codes 433 to 434 or ICD-10 code I63) or (2) a hemorrhagic stroke (ICD-9 codes 430 to 431 or ICD-10 codes I60-I61) based on results from CT, MRI and/or autopsy. We used Cox proportional hazard adjusted models to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of ePWV for incident stroke.

Results

During a median 28-year follow-up, 471 incident stroke events occurred (comprising of 397 ischemic stroke and 94 hemorrhagic stroke). Twenty events were diagnosed as both ischemic and hemorrhagic stroke. After adjusting for potential confounders (age, body mass index, smoking, alcohol intake, CVD history, anti-hypertensive medication, glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, C-reactive protein, creatinine, physical activity, socioeconomic status, diabetes, family history of CVD), the highest levels of ePWV were associated with an increased risk for stroke (hazard ratio [HR] 2.41, 95% Confidence Interval [CI]: 1.66-3.53), ischemic stroke (HR 2.35, 95% CI, 1.56-3.56), and hemorrhagic stroke (HR 3.29, 95% CI, 1.44-7.52), compared with the lowest level of ePWV (Table 1). The associations were not attenuated following further adjustment for pulse pressure (or systolic blood pressure in a separate model). Cumulative hazard curves demonstrated higher incidence of stroke in the top quartile of ePWV compared to the bottom quartile ($P<0.001$ for log-rank test; Figure 1).

Discussion

These findings demonstrate that ePWV is related to increased risk for cerebrovascular outcomes, independent of several traditional and emerging CVD risk factors including age and pulse pressure.

Previous studies note that cfPWV is associated with stroke risk.(7, 15) Our study supports emerging findings of an association between ePWV and overall stroke risk (3, 6) and suggests that ePWV is also associated with stroke subtypes - ischemic and hemorrhagic stroke. Compared to the reference group, individuals in the elevated ePWV group were almost 3.6 times more likely to have a hemorrhagic stroke and 2.2 times more likely to have an ischemic stroke, after adjustment for confounding CVD risk factors including age and pulse pressure.

An increase in ePWV may be associated with increased risk for stroke (both ischemic and hemorrhagic) through several speculative mechanisms. Arterial stiffness-mediated increases in pressure pulsatility may lead to altered hemodynamic stress, aneurysm and cerebral vessel rupture (16, 17) and may also contribute to epochs of cerebral hypoperfusion and ischemia, cerebrovascular endothelial damage, altered shear patterns, and atherogenesis.(18, 19) However, we noted that risk estimates between ePWV and stroke remained similar after additional adjustment for PP. This is consistent with findings from Laurent *et al.* and Mattace-Raso *et al.* that noted cfPWV was associated with stroke risk after adjusting for traditional CVD risk factors including PP.(7, 8) Brachial PP is not a reflection of central PP or the regional pressure that may be experienced by the cerebrovasculature. Thus, pressure pulsatility cannot be discounted as an important effector of cerebrovascular structure and function. Alterations in vessel wall stiffness captured by ePWV may reflect systemic arteriosclerosis from fibrosis and calcification and thus parallel lesion development in the cerebrovasculature.(7, 8) Loss of vessel wall compliance may also directly impact regional vessel wall shear contributing to ulceration of vulnerable plaque.(20) It should be underscored that this study is one of association and no conclusion on underlying mechanism is possible.

Limitations of this study include a cohort that comprised exclusively middle-aged Caucasian men of European decent and inability to explore BP variability and changes in BP-lowering treatment due to lack of relevant data. Additional research evaluating the associations and predictive relevance in women and other races/ethnicities is warranted. In summary, ePWV is a simple measure derived from two commonly assessed clinical parameters (age and BP) that may offer insight into incident stroke risk in middle-aged men.

References

1. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology 2019;18(5):439-58.
2. Liu FD, Shen XL, Zhao R, et al. Pulse pressure as an independent predictor of stroke: a systematic review and a meta-analysis. Clinical research in cardiology : official journal of the German Cardiac Society 2016;105(8):677-86.
3. Vlachopoulos C, Terentes-Printzios D, Laurent S, et al. Association of Estimated Pulse Wave Velocity With Survival: A Secondary Analysis of SPRINT. JAMA network open 2019;2(10):e1912831.
4. Heffernan KS, Jae SY, Loprinzi PD. Association Between Estimated Pulse Wave Velocity and Mortality in U.S. Adults. Journal of the American College of Cardiology 2020;75(15):1862-4.
5. Jae SY, Heffernan KS, Park JB, et al. Association between estimated pulse wave velocity and the risk of cardiovascular outcomes in men. European journal of preventive cardiology 2020:2047487320920767.
6. Vishram-Nielsen JKK, Laurent S, Nilsson PM, et al. Does Estimated Pulse Wave Velocity Add Prognostic Information?: MORGAM Prospective Cohort Project. Hypertension (Dallas, Tex : 1979) 2020;75(6):1420-8.
7. Laurent S, Katsahian S, Fassot C, et al. Aortic Stiffness Is an Independent Predictor of Fatal Stroke in Essential Hypertension. Stroke 2003;34(5):1203-6.
8. Mattace-Raso Francesco US, van der Cammen Tischa JM, Hofman A, et al. Arterial Stiffness and Risk of Coronary Heart Disease and Stroke. Circulation 2006;113(5):657-63.
9. Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. Ann Clin Res 1988;20(1-2):46-50.
10. Greve SV, Blicher MK, Kruger R, et al. Estimated carotid-femoral pulse wave velocity has similar predictive value as measured carotid-femoral pulse wave velocity. Journal of hypertension 2016;34(7):1279-89.
11. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. European heart journal 2010;31(19):2338-50.
12. Kurl S, Laukkanen JA, Tuomainen TP, et al. Association of exercise-induced, silent ST-segment depression with the risk of stroke and cardiovascular diseases in men. Stroke 2003;34(7):1760-5.
13. Tuomilehto J, Rastenyte D, Sivenius J, et al. Ten-year trends in stroke incidence and mortality in the FINMONICA Stroke Study. Stroke 1996;27(5):825-32.
14. Kurl S, Laukkanen JA, Niskanen L, et al. Metabolic syndrome and the risk of stroke in middle-aged men. Stroke 2006;37(3):806-11.
15. Pereira T, Maldonado J, Pereira L, Conde J. A distensibilidade da aorta prediz o acidente vascular cerebral em pacientes hipertensos. Arquivos Brasileiros de Cardiologia 2013;100:437-43.
16. Matsukawa H, Shinoda M, Fujii M, Uemura A, Takahashi O, Niimi Y. Arterial stiffness as a risk factor for cerebral aneurysm. Acta neurologica Scandinavica 2014;130(6):394-9.
17. Lefferts WK, Heffernan KS. Cerebral hemodynamics and intracranial aneurysms: Reflecting on pipeline embolization devices. Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences 2018;24(6):631-4.
18. Tarumi T, Shah F, Tanaka H, Haley AP. Association Between Central Elastic Artery Stiffness and Cerebral Perfusion in Deep Subcortical Gray and White Matter. American Journal of Hypertension 2011;24(10):1108-13.

19. Hansen L, Taylor WR. Is increased arterial stiffness a cause or consequence of atherosclerosis? Atherosclerosis 2016;249:226-7.
20. Selwaness M, van den Bouwhuijsen Q, Mattace-Raso FU, et al. Arterial stiffness is associated with carotid intraplaque hemorrhage in the general population: the Rotterdam study. Arteriosclerosis, thrombosis, and vascular biology 2014;34(4):927-32.

Table 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident stroke outcomes by ePWV quartiles.

ePWV	Hemorrhagic stroke	Ischemic stroke	Total stroke
	Events/Total	Events/Total	Events/Total
All	94/2666	397/2666	471/2666
Q 1 (< 8.5 m/s)	14/637	49/637	59/637
Q 2 (8.5-9.2 m/s)	18/643	83/643	95/643
Q 3 (9.2-10.0 m/s)	29/694	121/694	147/694
Q 4 (>10.0 m/s)	33/692	144/692	170/692
Model 1, Adjusted for age, body mass index, smoking, alcohol intake, CVD history, anti-hypertensive medication use, glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, C-reactive protein, creatinine, physical activity, socioeconomic status, diabetes, family history of CVD			
Each 1 m/s increment	1.53 (1.22-1.92)	1.32 (1.18-1.49)	1.35 (1.21-1.49)
Q 1	1 (reference)	1 (reference)	1 (reference)
Q 2	1.20 (0.54-2.67)	1.34 (0.90-1.99)	1.28 (0.89-1.84)
Q 3	2.47 (1.14-5.33)	2.05 (1.39-3.02)	2.10 (1.47-3.00)
Q 4	3.29 (1.44-7.52)	2.35 (1.56-3.56)	2.41 (1.66-3.53)
Model 2, Model 1 plus pulse pressure			
Each 1 m/s increment	1.69 (1.27-2.25)	1.34 (1.16-1.54)	1.38 (1.22-1.58)
Q 1	1 (reference)	1 (reference)	1 (reference)
Q 2	1.22 (0.55-2.73)	1.32 (0.89-1.97)	1.27 (0.88-1.83)
Q 3	2.57 (1.17-5.66)	1.99 (1.34-2.97)	2.08 (1.45-2.99)
Q 4	3.57 (1.45-8.76)	2.23 (1.42-3.50)	2.37 (1.57-3.58)
Model 3, Model 1 plus systolic blood pressure			
Each 1 m/s increment	2.35 (1.17-4.75)	1.39 (0.99-1.94)	1.50 (1.10-2.05)
Q 1	1 (reference)	1 (reference)	1 (reference)
Q 2	1.11 (0.47-2.61)	1.21 (0.80-1.85)	1.17 (0.80-1.73)
Q 3	2.16 (0.84-5.54)	1.72 (1.08-2.74)	1.81 (1.18-2.78)
Q 4	2.61 (0.74-9.21)	1.72 (0.92-3.20)	1.85 (1.04-3.28)

CVD, cardiovascular disease; ePWV, estimated pulse wave velocity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q, quartile

Figure 1. The Kaplan-Meier curves for incident stroke by ePWV quartiles.