Jae, S. Y., Heffernan, K., Kurl, S., Kunutsor, S. K., & Laukkanen, J. (2021). Association Between Estimated Pulse Wave Velocity and the Risk of Heart Failure in the Kuopio Ischemic Heart Disease Risk Factor Study: Estimated pulse wave velocity and the risk of heart failure. *Journal of Cardiac Failure*, 27(4), 494-496.
<https://doi.org/10.1016/j.cardfail.2020.11.012>

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Association Between Estimated Pulse Wave Velocity and the Risk of Heart Failure in the Kuopio Ischemic Heart Disease Risk Factor Study

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Running title: Estimated pulse wave velocity and the risk of heart failure

Disclosures: none

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Background: Increased aortic stiffness, assessed as carotid-femoral pulse wave velocity (cfPWV), is associated with incident heart failure risk.

Methods and Results: We examined the association between estimated pulse wave velocity (ePWV), derived from a regression equation using age and mean arterial pressure, and incident heart failure risk in a prospective cohort of 2,465 men (age range 42-61 years) enrolled in the Kuopio Ischemic Heart Disease cohort study. During a median follow-up of 26 years, 431 heart failure events occurred. After adjusting for potential confounders (age, pulse pressure, body mass index, smoking, alcohol consumption, diabetes, history of cardiovascular disease (CVD), family history of CVD, use of medications [anti-hypertensive agents and lipid-lowering drugs], total cholesterol, high density lipoprotein-cholesterol, triglycerides, glucose, C-reactive protein, creatinine, socioeconomic status, and physical activity), the highest levels of ePWV (≥ 10 m/s) were significantly associated with an increased risk of heart failure (HR 2.04, 95% CI: 1.29-3.21), compared with the lowest level of ePWV (< 8.5 m/s).

Conclusion: Increased ePWV is related to future heart failure risk, independent of several traditional CVD risk factors, in middle-aged men.

Key Words: carotid-femoral pulse wave velocity, heart failure

Blood pressure (BP), which is a risk factor for heart failure (HF), has both steady and pulsatile components. 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 cardiovascular disease (CVD) outcomes, including HF.[1] Recently, another BP-derived measure of large artery stiffening and CVD risk has emerged.[2] The current gold-standard method for the assessment of aortic stiffness is carotid-femoral pulse wave velocity (cfPWV). A number of studies indicate that cfPWV is associated with the risk of future HF.[3, 4] cfPWV can be estimated from a regression equation utilizing age and mean blood pressure.[2] This estimated pulse wave velocity (ePWV) has similar relative CVD predictive value as cfPWV,[2] and is associated with cardiovascular outcomes and all-cause mortality in hypertensive adults [5] and in the general population.[6, 7] We sought to examine the association between ePWV and HF in the general population.

From a sample of 2,682 middle-aged men with mean (standard deviation, SD) age of 53.1 (5.1), range 42-61 years, who were recruited into the Kuopio Ischemic Heart Disease cohort study between March 1984 and December 1989, we excluded 194 men with a history of HF at baseline examinations and 23 men with missing information (n=7 for HF and n=16 for BP). Accordingly, 2,465 men who had complete data on ePWV, potential confounders (age, pulse pressure, body mass index, smoking, alcohol consumption, diabetes, CVD history, family history of CVD, use of medications [anti-hypertensive agents and lipid-lowering drugs], total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides, glucose, C-reactive protein, creatinine, socioeconomic status, and physical activity) and HF outcomes were included in the present analysis. 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) as follows [2, 5]:
$$\text{ePWV} = 9.587 - 0.402 \times \text{age} + 4.560 \times 10^{-3} \times \text{age}^2 - 2.621 \times 10^{-5} \times \text{age}^2 \times \text{MBP} + 3.176 \times 10^{-3} \times \text{age} \times \text{MBP} - 1.832 \times 10^{-2} \times \text{MBP}.$$
 Mean blood pressure (MBP) was calculated as diastolic blood pressure + 0.4 * PP with PP being taken as systolic blood pressure (SBP) – diastolic blood pressure (DBP). 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]). New incident cases of HF were obtained from the National Hospital Discharge Register data with events coded according to ICD-10 codes (I50.0-I50.9, I11,I42.0-I42.9) following standard clinical investigation and European Task Force guidelines.[8] We included all HF events that occurred from study enrollment through to 2018. We used Cox proportional hazard multivariable adjusted models to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of ePWV for incident HF. First, we adjusted for the constituent components of ePWV (age and PP) to assess the predictive capacity of ePWV beyond its derivatives. We then adjusted for established traditional CVD and HF risk factors.

During a median follow-up of 26 years, 431 HF events occurred. Cumulative hazard curves demonstrated higher incidence of HF in the top quartile of ePWV compared to the bottom quartile ($P<0.001$ for log-rank test; Figure 1).

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

After adjusting for potential confounders (defined above), the highest levels of ePWV were significantly associated with an increased risk of HF (HR 2.04, 95% CI: 1.29-3.21), compared with the lowest level of ePWV (Table 1). Each 1 m/s increase in ePWV was associated with a 17% (HR 1.17, 95% CI: 1.02-1.34) increase in the risk of HF after adjusting for the above confounders. Supplemental Table 1 shows respective hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of the individual confounders with the risk of incident HF. Supplemental Table 2 reports the proportion of missing data.

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

Variables	Events/total	Model 1	Model 2	Model 3
	431/2465	HR (95% CI)	HR (95% CI)	HR (95% CI)
Each 1m/s increment		1.41 (1.27-1.55)	1.34 (1.18-1.51)	1.17 (1.02-1.34)
< 8.5 m/s	42/609	1 (ref)	1 (ref)	1 (ref)
8.5-9.2 m/s	100/594	1.86 (1.38-2.71)	1.79 (1.23-2.61)	1.60 (1.07-2.39)
9.2-10.0 m/s	132/647	2.31 (1.58-3.36)	2.15 (1.46-3.15)	1.86 (1.23-2.80)
> 10.0 m/s	157/615	3.30 (2.24-4.86)	2.80 (1.85-4.24)	2.04 (1.29-3.21)

Model 1: Adjusted for age

Model 2: Adjusted for age and pulse pressure.

Model 3, Adjusted for Model 2 plus body mass index, smoking, alcohol consumption, diabetes, CVD history, family history of CVD, use of medications (anti-hypertensive agents and lipid-lowering drugs), total cholesterol, HDL-C, triglycerides, glucose, C-reactive protein, creatinine, socioeconomic status, and physical activity.

These findings demonstrate that increased ePWV is related to future HF risk, independent of several traditional and emerging CVD risk factors, including age and PP, in the general population. Independently of the effects of PP, vascular wall stiffness may impact afterload and loading sequence, serving as the substrate for myocardial dysfunction and detrimental left ventricular remodeling.[9] Our study supports previous findings of an association between ePWV and HF in adults with a history of hypertension. Vlachopoulos *et al.* noted that for each one SD increase in ePWV, there was a 1.7 times greater risk of incident HF in SPRINT trial participants.[5] Compared to the reference group, individuals in the elevated ePWV group in the current study were approximately 2 times more likely to develop HF, after adjustment for several traditional and emerging risk factors including age and pulse pressure.

A limitation of this study is that the cohort examined comprised exclusively Caucasian men of European decent. Moreover, information on HF subtypes (i.e. HFpEF vs HFrEF) was

not available. Given that the prevalence of HF is higher in Black individuals and men and women present with different HF phenotypes, additional research evaluating the associations and predictive relevance of ePWV in women and other races/ethnicities as well as across HF phenotypes is warranted. In summary, higher ePWV is strongly and independently associated with increased risk of future HF. The assessment of ePWV is easy and inexpensive and can potentially be easily be utilized in clinical practice settings to aid in HF risk prediction.

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Supplemental Table 1. Multivariable-adjusted HRs (95% CIs) of individual confounders for incident HF

Variables	HR (95% CI)	P-value
ePWV	1.17 (1.02-1.34)	0.025
Age	1.10 (1.07-1.14)	<0.001
Pulse pressure	1.01 (0.99-1.02)	0.073
Body mass index	1.08 (1.05-1.16)	<0.001
Smoking (yes)	1.73 (1.38-2.18)	<0.001
Alcohol consumption	1.00 (0.99-1.00)	0.926
Diabetes (yes)	1.33 (0.83-2.15)	0.237
History of CVD (yes)	1.51 (1.22-1.88)	<0.001
Anti-hypertensive agents (yes)	1.85 (1.46-2.34)	<0.001
Family history of CVD (yes)	1.19 (0.97-1.45)	0.097
Lipid-lowering drugs (yes)	1.19 (0.37-3.81)	0.767
HDL-cholesterol	0.98 (0.67-1.44)	0.936
Glucose	1.14 (1.04-1.25)	0.005
Creatinine	1.00 (0.99-1.01)	0.883
Total cholesterol,	1.07 (0.97-1.17)	0.180
Triglycerides	0.92 (0.78-1.09)	0.322
C-reactive protein	1.02 (0.99-1.05)	0.063
Socioeconomic status*	1.06 (1.04-1.09)	<0.001
Physical activity	1.00 (1.00-1.00)	0.514

*High score represents low SES.

Supplemental Table 2. A list of the missing variables and the proportion missing

Variables	Missing	Total	Percent Missing
ePWV	0	2,465	0.00
Age	0	2,465	0.00
Pulse pressure	0	2,465	0.00
Body mass index	0	2,465	0.00
Smoking (yes)	0	2,465	0.00
Alcohol consumption	0	2,465	0.00
Diabetes (yes)	0	2,465	0.00
History of CVD (yes)	0	2,465	0.00
Anti-hypertensive agents (yes)	0	2,465	0.00
Family history of CVD (yes)	0	2,465	0.00
Lipid-lowering drugs (yes)	0	2,465	0.00
HDL-cholesterol	34	2,431	1,38
Glucose	22	2,443	0,89
Creatinine	32	2,433	1,30
Total cholesterol,	0	2,465	0.00
Triglycerides	66	2,399	0.00
C-reactive protein	41	2,424	1,66
Socioeconomic status	0	2,465	0.00
Physical activity	9	2,456	0,37