Pulse Wave Velocity Predicts the Progression of Blood Pressure and Development of Hypertension in Young Adults

Teemu Koivistoinen, Leo-Pekka Lyytikäinen, Heikki Aatola, Tiina Luukkaala, Markus Juonala, Jorma Viikari, Terho Lehtimäki, Olli T. Raitakari, Mika Kähönen, Nina Hutri-Kähönen

Abstract—The aim of the present study was to examine whether pulse wave velocity (PWV) predicts the progression of blood pressure and the development of hypertension in young adults. In addition, we studied whether PWV improves the risk prediction of incident hypertension beyond traditional cardiovascular risk factors. Systolic and diastolic blood pressures were measured in 2007 and 2011 for 1449 Finnish adults (aged 30–45 years). In addition, PWV and other cardiovascular risk factors were measured in 2007. The association between PWV (in 2007) and blood pressure (in 2011) was studied in the whole population (n=1449) and in a normotensive subpopulation (n=1183). The ability of PWV measured in 2007 to predict incident hypertension in 2011 was investigated in the subpopulation (n=1183). PWV measured in 2007 was directly and independently associated with systolic and diastolic blood pressures measured in 2011 (P<0.001 for both). PWV measured in 2007 was also an independent predictor of incident hypertension in 2011 (odds ratio, 1.96 per 1-SDincrease; 95% confidence interval, 1.51–2.57; P<0.001). The extended prediction model (including PWV) improved the incident hypertension risk prediction beyond traditional cardiovascular risk factors, the area under receiver operating characteristics curve being 0.833 versus 0.809 (P=0.040), and the continuous net reclassification improvement 59.4% (P<0.001). These findings suggest that PWV predicts the progression of blood pressure and could provide a valuable tool in hypertension risk prediction in young adults. **(*Hypertension*. 2018;71:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.10368.)** ● **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular diseases ■ hypertension ■ risk factors ■ vascular stiffness

Cardiovascular diseases are the leading cause of death, accounting for almost a third of global deaths.[1] The complications of hypertension are responsible for more than half of these, and therefore, the World Health Organization has stated that the prevention and control of hypertension is one of the most important ways to reduce deaths and disability from noncommunicable diseases.[2]

As a widely used marker of arterial stiffness, pulse wave velocity (PWV) is a robust predictor of cardiovascular events and mortality.[3] Increased PWV is also regarded as a marker of asymptomatic organ damage in the European Society of Hypertension and the European Society of Cardiology guidelines for the management of arterial hypertension.[4] Elevated blood pressure has been shown to associate with PWV in several studies,[5–7] and it has, therefore, been previously assumed that adverse alterations in the vascular wall caused by hypertension lead to arterial stiffening.[8,9] However, contrary to this assumption, a recent scientific statement from the American Heart Association[9] suggests that there is strong evidence in support of the hypothesis that arterial stiffness represents a cause rather than a consequence of hypertension. This evidence includes the notion that PWV predicts the increase in blood pressure and onset of hypertension in middle-aged and older individuals.[10–13]

Previous studies examining the association between PWV and longitudinal changes in blood pressure have been conducted on individuals aged from 53±17 to 60±9 years (mean±SD).[10–13] The objective of the present study was to evaluate whether PWV predicts an increase in blood pressure and the development of hypertension in young adults (aged 38±5 years). Another aim was to study whether PWV improves the risk prediction of incident hypertension beyond traditional cardiovascular risk factors.

Methods

The study was conducted according to the guidelines of the Declaration of Helsinki, and the study was approved by local ethics

Received September 22, 2017; first decision October 4, 2017; revision accepted December 14, 2017.

From the Departments of Clinical Physiology (T.K., H.A., M.K.), Clinical Chemistry, Fimlab Laboratories (L.-P.L., T. Lehtimäki), and Pediatrics (N.H-K.), Faculty of Medicine and Life Sciences, University of Tampere and Tampere University Hospital, Finland; Department of Emergency Medicine, Kanta-Häme Central Hospital, Hämeenlinna, Finland (T.K.); Research and Innovation Center, Tampere University Hospital, Finland (T. Luukkaala); Health Sciences, Faculty of Social Sciences, University of Tampere, Finland (T. Luukkaala); Department of Medicine (M.J., J.V.) and Research Centre of Applied and Preventive Cardiovascular Medicine (O.T.R.), University of Turku, Finland; and Division of Medicine (M.J., J.V.) and Department of Clinical Physiology and Nuclear Medicine (O.T.R.), Turku University Hospital, Finland.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.117.10368/-/DC1.

Correspondence to Teemu Koivistoinen, Department of Clinical Physiology, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland. E-mail teemu.koivistoinen@outlook.com

committees. Informed written consent was obtained from all subjects. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The Cardiovascular Risk in Young Finns Study is an on-going large multicenter study of cardiovascular risk factors in Finland. The study design and protocol have been described in detail previously.[14] In brief, the first cross-sectional study was conducted in 1980 with 3596 participants aged 3 to 18 years. Several follow-up studies have been performed thereafter. In 2007, 1872 men and women participated in PWV measurement, and 1501 of them also had blood pressure data available in 2011. After excluding subjects with incomplete cardiovascular risk factor data from 2007, a total of 1449 men and women were included in the present analysis. A subpopulation of 1183 men and women was comprised those subjects who were normotensive in 2007. The association between PWV measured in 2007 and blood pressure measured in 2011 was studied in both populations. Association between PWV measured in 2007 and incident hypertension in 2011 was examined in the subpopulation of participants who were normotensive in 2007 (n=1183).

Blood Pressure Measurement and Clinical Characteristics

Blood pressure from the right brachial artery was measured in the sitting position after a 5-minute rest with a random-zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, United Kingdom) in 2007 and 2011 as described previously.[15] The average of 3 measurements was used in the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg,[4] self-reported use of antihypertensive medication, or a self-reported hypertension diagnosis.

Body mass index (BMI, kg/m^2) was calculated by dividing the weight in kilograms by the square of the height in meters. Venous blood samples were collected after an overnight fast. Standard methods were used to determine serum high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, C-reactive protein, insulin, and glucose concentrations.[16,17] Smoking habits were examined with a questionnaire, and the subjects who were smoking daily were regarded as smokers.

Pulse Wave Velocity

PWV was measured between the aortic arch and the popliteal artery by the commercially available whole-body impedance cardiography device (CircMon). To minimize the effects of sympathetic activity on PWV measurements, participants lay in supine position for at least 15 minutes prior the measurement. Moreover, participants were instructed to avoid heavy exercise and alcohol on the previous evening, and smoking, caffeine-containing products, and heavy meals in the investigation day. A pair of electrically connected current electrodes was applied to the wrists and ankles, and a pair of voltage electrodes was placed 5 cm proximally to the current electrodes. In the whole-body impedance cardiography measurement, the current electrodes apply current and the voltage electrodes measure the changes in impedance induced by the heart-synchronous pulsation. The foot of the whole-body impedance signal coincides with pulse transmission in the aortic arch. An additional pair of voltage electrodes was applied at the knee joint level and the calf. The foot of the impedance signal measured at this location coincides with the pulse transmission in the popliteal artery. By means of the measured transit time from the aortic arch to the popliteal artery, and the estimated distance between these 2 sites, the CircMon software calculates the PWV. A more detailed description of the method,[6,18] a validation study,[18] reference values,[19] good repeatability and reproducibility indexes,[20] and a good correlation with the tonometric method (carotid–femoral PWV)[21] have been published previously.

Statistics

The data were analyzed with R Statistics version 3.2.4 (R Development Core Team, Vienna, Austria). Linear regression was performed to study the association between PWV measured in 2007 and blood pressure measured in 2011. Separate analyses were made of both populations (whole population and normotensive subpopulation). Logistic regression analysis was used to study the association of PWV measured in 2007 with hypertension in 2011. Logistic regression was performed on 1183 subjects who were normotensive in 2007. The regression models additionally included traditional cardiovascular risk factors measured in 2007 (age, sex, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, insulin, BMI, smoking, C-reactive protein, heart rate, and systolic and diastolic blood pressures). The skewed distributions of PWV, C-reactive protein, insulin, and triglycerides were log transformed. All continuous predictor variables besides age were standardized to make the predictor variable effect sizes comparable to each other. Therefore, the regression coefficients (β) in the linear regression models and the odds ratio in the logistic regression model indicate the effect of a 1-SD change in a predictor variable on a given dependent variable. The effects of sex by age by BMI interactions on hypertension in 2011 were tested using the stepwise Akaike Information Criterion. There were no statistically significant interactions between sex, age, or BMI and hypertension in 2011. Before the analyses, regression models were assessed for excess multicolinearity by stepwise variance inflation factor selection. All of the variables had a variance inflation factor <10 and, therefore, the variables were included in the model simultaneously.

To study whether PWV measured in 2007 improves the incident hypertension risk prediction in 2011, the area under the receiver operating characteristic curve and continuous net reclassification improvement[22,23] were calculated. The first model included only traditional cardiovascular risk factors, whereas the second model included traditional risk factors and PWV. Furthermore, the potential additional value of PWV was assessed by the risk assessment plot.[24] A $P<.05$ was considered statistically significant.

Results

The baseline (2007) characteristics of the whole study population (n=1449) and the subpopulation of normotensive subjects (n=1183) are presented in Table 1. Between 2007 and

Table 1. Baseline (2007) Characteristics of Study Subjects

Variable	Whole Population (n=1449)	Normotensive Subpopulation (n=1183)
Age, y	38.0±5.0	37.4±5.0
Sex (% female)	56	58
Systolic blood pressure, mm Hg	120±14	116±11
Diastolic blood pressure, mm Hg	75±11	72±9
HDL cholesterol, mmol/L	1.3±0.3	1.3±0.3
LDL cholesterol, mmol/L	3.1±0.8	3.0±0.8
Triglycerides, mmol/L	1.1 (0.8–1.6)	1.1 (0.8–1.5)
Body mass index, kg/m^2	26±5	25±4
C-reactive protein, mg/L	0.9 (0.4–1.8)	0.8 (0.4–1.6)
Insulin, mU/L	6.6 (4.2–10.3)	6.1 (4.0–9.7)
Glucose, mmol/L	5.3±0.7	5.2±0.5
Hypertension (% of subjects)	18	…
Smoking (% of subjects)	17	18
Pulse wave velocity, m/s	7.9 (7.1–9.0)	7.4 (6.7–8.2)

Values are presented as mean±SD or geometric mean (25th–75th percentiles) or percentages of subjects. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

2011, a statistically significant difference was observed in systolic blood pressure in the whole population (120±14 versus 119±14 mm Hg; P=0.01) and in diastolic blood pressure in the subpopulation (72±9 versus 73±9 mm Hg; P=0.03). In the subpopulation of subjects who were normotensive in 2007, 88 (7.4%) subjects had incident hypertension in 2011.

In both populations, PWV measured in 2007 was directly and independently associated with systolic and diastolic blood pressures measured in 2011 (Table 2). An increase of 1 SD in PWV was associated with a 2.75- to 2.96-mm Hg increase in systolic blood pressure measured in 2011 (P<0.001). For diastolic blood pressure, the increase was 2.09 to 2.29 mm Hg (P<0.001; Table 2). Between 2007 and 2011, 53 participants in the whole population and 20 participants in the subpopulation initiated blood pressure–lowering medication. When initiation of blood pressure–lowering medication was included in the linear regression analysis as a dichotomous variable, in the whole population initiation of medication was independently associated with systolic and diastolic blood pressures measured in 2011 (Table S1 in the online-only Data Supplement). In the subpopulation, association between initiation of antihypertensive medication and systolic or diastolic blood pressure was not statistically significant.

In multivariable logistic regression analysis, PWV measured in 2007 was the second highest predictor of incident hypertension in 2011 (odds ratio, 1.96 [95% confidence interval, 1.51–2.57; P<0.001]; Table 3). When more stringent blood pressure cutoffs were used to define hypertension (systolic blood pressure ≥120 mm Hg or diastolic blood pressure ≥80 mm Hg), PWV measured in 2007 was the highest predictor of incident hypertension in 2011 (odds ratio, 2.16 [95% confidence interval, 1.72–2.75; P<0.001]; Table S2).

Two models were compared for their ability to classify participants into the healthy and incident hypertension categories in 2011 (Table 4). The first model included sex and age, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, insulin, heart rate, BMI, smoking, C-reactive protein, and systolic and diastolic blood pressures measured in 2007. The second model additionally included PWV. The second model had a higher area under the receiver operating characteristic curve (0.833) than the first model (0.809; P=0.040). The continuous net reclassification improvement for the second model was 59.4% (P<0.001; Table 4). Essentially, similar results were obtained when more stringent blood pressure cutoffs were used to define hypertension (systolic blood pressure ≥120 mm Hg or diastolic blood pressure ≥80 mm Hg; Table S3). The risk assessment plot

Table 2. Associations of Risk Factors Measured in 2007 With Blood Pressure Measured in 2011

Whole Population (n=1449)			Subpopulation (n=1183)		
Variables Measured in 2007	β±SE	*P* Value	Variables Measured in 2007	β±SE	*P* Value
Systolic blood pressure measured in 2011					
Systolic blood pressure	7.53±0.44	<0.001	Systolic blood pressure	5.48±0.40	<0.001
PWV	2.96±0.33	<0.001	PWV	2.75±0.33	<0.001
BMI	1.17±0.36	<0.001	Sex	1.99±0.71	0.005
Diastolic blood pressure	−1.16±0.42	0.006	Smoking	1.78±0.75	0.017
Insulin	0.72±0.36	0.045	BMI	1.46±0.36	<0.001
Age	0.23±0.06	<0.001	Heart rate	0.68±0.30	0.025
			Age	0.23±0.06	<0.001
Diastolic blood pressure measured in 2011					
Diastolic blood pressure	3.56±0.32	<0.001	Diastolic blood pressure	2.58±0.29	<0.001
PWV	2.29±0.25	<0.001	PWV	2.09±0.25	<0.001
Sex	1.94±0.51	<0.001	Sex	2.02±0.55	0.001
BMI	1.03±0.27	<0.001	BMI	1.33±0.28	<0.001
Systolic blood pressure	0.80±0.34	0.017	Heart rate	0.72±0.23	0.002
Glucose	−0.77±0.23	<0.001	Age	0.15±0.05	0.001
Heart rate	0.55±0.22	0.013			
Age	0.13±0.04	0.003			

Multivariable models included sex and age, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, insulin, body mass index (BMI), smoking, C-reactive protein, heart rate, systolic and diastolic blood pressures, and pulse wave velocity (PWV) measured in 2007. Variables with a statistically significant association with blood pressure are reported. All continuous predictive variables, expect age, were standardized before regression analysis. Regression coefficient β indicates the change in systolic or diastolic blood pressure measured in 2011 when a variable measured in 2007 changed by 1 SD. For sex and smoking, β indicates the change in systolic or diastolic blood pressure measured in 2011 when category changed in 2007. Subpopulation: subjects normotensive in 2007.

Table 3. Relationship Between Variables Measured in 2007 and Hypertension in 2011

	Hypertension in 2011	
Variables Measured in 2007	OR (95% CI)	*P* Value
Smoking	2.38 (1.31–4.23)	0.004
PWV	1.96 (1.51–2.57)	<0.001
Diastolic blood pressure	1.74 (1.23–2.50)	0.002
Systolic blood pressure	1.38 (0.98–1.94)	0.063
Age	1.08 (1.03–1.14)	0.002

The multivariable model included sex and age, as well as high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, insulin, body mass index, smoking, C-reactive protein, heart rate, systolic and diastolic blood pressures, and pulse wave velocity (PWV) measured in 2007. Variables with a statistically significant or borderline significant (P<0.08) association with hypertension are reported. Analyses performed on 1183 subjects who were normotensive in 2007. Eighty-eight (7.4%) of these subjects had hypertension in 2011. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported use of antihypertensive medication, or self-reported hypertension diagnosis. CI indicates confidence interval; OR, odds ratio per 1-SD increase in predictor variable, except for smoking per change in category (nonsmoker/smoker); and PWV, pulse wave velocity.

Table 4. Comparison of Models for the Prediction of Incident Hypertension

Model	AUC	95% CI	*P* Value	NRI Events (%)	*P* Value	NRI Nonevents (%)	*P* Value	NRI Total (%)	*P* Value
Reference model	0.809	0.767–0.851	…	…	…	…	…	…	…
Reference model+PWV	0.833	0.795–0.872	0.040	29.6	0.004	29.9	<0.001	59.4	<0.001

Reference model: age, sex, smoking, systolic and diastolic blood pressures, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, insulin, heart rate, and C-reactive protein measured in 2007. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported use of antihypertensive medication, or self-reported hypertension diagnosis. AUC indicates area under the receiver operating characteristic curve; CI, confidence interval; event, incident hypertension; NRI, continuous net reclassification improvement; and PWV, pulse wave velocity.

supported the additional value of PWV in the incident hypertension risk assessment (Figure).

Discussion

The present study examining the effects of PWV on the progression of blood pressure and the development of hypertension among young Finnish adults produced 3 main findings. First, PWV measured in 2007 was directly and independently associated with an increase in blood pressure in 2011. Second, PWV independently predicted the development of hypertension. Third, PWV measured 4 years earlier improved the incident hypertension risk prediction beyond traditional cardiovascular risk factor.

It has been previously shown in middle-aged and older populations that carotid–femoral[10,12] and brachial–ankle[11,13] PWV are related to future blood pressure levels and incident hypertension. Conversely, initial blood pressure levels were not found to associate with future carotid–femoral[12] or brachial–ankle[13] PWV. Therefore, based on these and other studies using different methods to evaluate arterial stiffness,[25,26] a recent scientific statement by the American Heart Association suggests that arterial stiffness represents a cause rather than a consequence of hypertension.[9] The present study supported this view by showing that PWV is directly and independently associated with blood pressure progression and incident hypertension among young adults. Although the mechanism between arterial stiffening and the development of hypertension is incompletely known, Mitchell[8] has provided a plausible explanation. With aging, the aorta dilates and a greater fraction of stress is transferred from elastin to the more rigid collagen in the arterial wall.[8,27] In younger subjects, although arterial wall stiffness is already increased, the aorta's dilation may reduce the pressure pulsatility.[8] Later in life, pulse pressure will begin to rise in proportion to the increase in PWV because the effect of dilation is attenuated by the growing amount of stress shifted from elastin to collagen.[8]

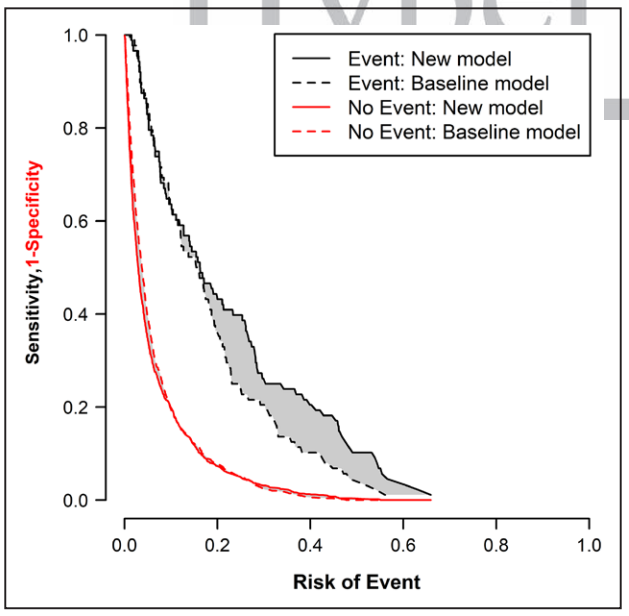

Figure. Additional value of pulse wave velocity (PWV) compared with the baseline (reference) model for the prediction of incident hypertension. Risk assessment plot for baseline (reference) model (dashed lines) and new model including PWV (solid lines). Event curves (black lines) represent sensitivity vs calculated risk. No event curves (red lines) represent 1-specificity vs calculated risk. Baseline (reference) model: age, sex, smoking, systolic and diastolic blood pressures, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, insulin, heart rate, and C-reactive protein. New model: baseline (reference) model+PWV.

To the best of our knowledge, this is the first study to demonstrate that PWV measured 4 years earlier improves the classification of participants into the categories of healthy and incident hypertension. A continuous net reclassification improvement of 59.4% may be considered rather a strong improvement in reclassification when PWV is added to the model (in addition to traditional cardiovascular risk factors).[28] Therefore, our findings suggest that PWV could provide a valuable tool for future hypertension risk assessment in clinical practice.

In the current study, systolic and diastolic blood pressures were weaker predictors of incident hypertension than PWV. Moreover, age was the weakest predictor of incident hypertension with a modest odds ratio of 1.08. Similar findings have been reported previously,[11] and the present findings, therefore, provide further support for the incremental predictive value of PWV. It should be noted that smoking in 2007 was also a strong predictor of incident hypertension in 2011. This finding is in line with a previous study showing an increased incidence of hypertension among women who smoke at least 15 cigarettes per day.[29] Furthermore, it has been previously shown that smokers have higher arterial pulse wave reflections compared with nonsmokers.[30]

The current PWV measurement method should be discussed briefly. As reviewed by Parati and Salvi,[31] increase in sympathetic activity results in decreased distensibility (or increased stiffness) in muscular arteries. On the contrary, the

effect of sympathetic nervous activation on aortic stiffness is weak. Therefore, we may speculate that carotid–femoral PWV, a gold standard method to assess arterial stiffness, would be a better indirect measure of arterial wall mechanical properties than the current PWV measurement method, which includes not only elastic aorta, but also muscular femoral and popliteal arteries. However, Wilenius et al[21] have previously shown that the current PWV measurement method (CircMon) is well in agreement with tonometric (SphygmoCor) carotid–femoral PWV. Moreover, all efforts were made to minimize the effects of sympathetic activity on PWV measurement, as described in the Methods section. Furthermore, heart rate, as an indirect marker of sympathetic activity, was included in all of the statistical models. Therefore, we strongly think that the present results are comparable to the previous studies, particularly to those conducted by using the carotid–femoral PWV,[10,12] and that increased sympathetic activity may not be playing major role behind the finding.

A major limitation of the present study was the lack of PWV data in 2011. Therefore, we were not able to examine the effects of blood pressure and hypertension on PWV progression. However, the objective of the present study was to evaluate whether PWV measured 4 years earlier predicts an increase in blood pressure and the development of hypertension in young adults. Moreover, our aim was to study whether PWV improves the risk prediction of incident hypertension beyond traditional cardiovascular risk factors, which is also novel information to the best of our knowledge. Another potential limitation was that the blood pressure measurements were not ambulatory or home blood pressure measurements, which might have overestimated the actual blood pressure levels.[4]

Perspectives

Our current findings suggest that PWV directly and independently predicts an increase in blood pressure and the development of hypertension among young adults. Moreover, PWV improves incident hypertension risk prediction. PWV could, therefore, provide a valuable additional tool for future hypertension risk evaluation.

Acknowledgments

Research Nurse Pirjo Järventausta is acknowledged for her skillful technical assistance in pulse wave velocity measurements.

Sources of Funding

The Young Finns Study has been financially supported by the Academy of Finland: grants 286284, 134309, 126925, 121584, 124282, 129378, 117787, and 41071; the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); the Juho Vainio Foundation; the Paavo Nurmi Foundation; the Finnish Foundation for Cardiovascular Research; the Finnish Cultural Foundation; the Tampere Tuberculosis Foundation; the Emil Aaltonen Foundation; the Yrjö Jahnsson Foundation; the Signe and Ane Gyllenberg Foundation; and the Diabetes Research Foundation of the Finnish Diabetes Association

Disclosures

None.

References

1. World Health Organization. Global Status Report on Noncommunicable Diseases. 2014. http://www.who.int/nmh/publications/ncd-status-report-2014/en/. Accessed December 15, 2017.
2. World Health Organization. A Global Brief on Hypertension. Silent Killer, Global Public Health Crisis. 2013. http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/. Accessed December 15, 2017.
3. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55:1318–1327. doi: 10.1016/j.jacc.2009.10.061.
4. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219. doi: 10.1093/eurheartj/eht151.
5. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension*. 2009;54:1328–1336. doi: 10.1161/HYPERTENSIONAHA.109.137653.
6. Aatola H, Hutri-Kähönen N, Juonala M, Viikari JS, Hulkkonen J, Laitinen T, Taittonen L, Lehtimäki T, Raitakari OT, Kähönen M. Lifetime risk factors and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns study. *Hypertension*. 2010;55:806–811. doi: 10.1161/HYPERTENSIONAHA.109.145102.
7. Aatola H, Magnussen CG, Koivistoinen T, Hutri-Kähönen N, Juonala M, Viikari JS, Lehtimäki T, Raitakari OT, Kähönen M. Simplified definitions of elevated pediatric blood pressure and high adult arterial stiffness. *Pediatrics*. 2013;132:e70–e76. doi: 10.1542/peds.2012-3426.
8. Mitchell GF. Arterial stiffness and hypertension: chicken or egg? *Hypertension*. 2014;64:210–214. doi: 10.1161/HYPERTENSIONAHA.114.03449.
9. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T; American Heart Association Council on Hypertension. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension*. 2015;66:698–722. doi: 10.1161/HYP.0000000000000033.
10. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, Spurgeon HP, Ferrucci L, Lakatta EG. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol*. 2008;51:1377–1383. doi: 10.1016/j.jacc.2007.10.065.
11. Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sonoda H, Sato K, Kimura G. Brachial-ankle pulse wave velocity predicts increase in blood pressure and onset of hypertension. *Am J Hypertens*. 2011;24:667–673. doi: 10.1038/ajh.2011.19.
12. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA*. 2012;308:875–881. doi: 10.1001/2012.jama.10503.
13. Zheng X, Jin C, Liu Y, Zhang J, Zhu Y, Kan S, Wu Y, Ruan C, Lin L, Yang X, Zhao X, Wu S. Arterial stiffness as a predictor of clinical hypertension. *J Clin Hypertens (Greenwich)*. 2015;17:582–591. doi: 10.1111/jch.12556.
14. Raitakari OT, Juonala M, Rönnemaa T, et al. Cohort profile: the Cardiovascular Risk in Young Finns Study. *Int J Epidemiol*. 2008;37:1220–1226. doi: 10.1093/ije/dym225.
15. Oikonen M, Nuotio J, Magnussen CG, Viikari JS, Taittonen L, Laitinen T, Hutri-Kähönen N, Jokinen E, Jula A, Cheung M, Sabin MA, Daniels SR, Raitakari OT, Juonala M. Repeated blood pressure measurements in childhood in prediction of hypertension in adulthood. *Hypertension*. 2016;67:41–47. doi: 10.1161/HYPERTENSIONAHA.115.06395.
16. Raiko JR, Viikari JS, Ilmanen A, Hutri-Kähönen N, Taittonen L, Jokinen E, Pietikäinen M, Jula A, Loo BM, Marniemi J, Lehtimäki T, Kähönen M, Rönnemaa T, Raitakari OT, Juonala M. Follow-ups of the cardiovascular risk in Young Finns Study in 2001 and 2007: levels and 6-year changes in risk factors. *J Intern Med*. 2010;267:370–384. doi: 10.1111/j.1365-2796.2009.02148.x.
17. Juonala M, Saarikoski LA, Viikari JS, Oikonen M, Lehtimäki T, Lyytikäinen LP, Huupponen R, Magnussen CG, Koskinen J, Laitinen T, Taittonen L, Kähönen M, Kivimäki M, Raitakari OT. A longitudinal analysis on associations of adiponectin levels with metabolic syndrome and carotid artery intima-media thickness. The Cardiovascular Risk in

Young Finns Study. *Atherosclerosis*. 2011;217:234–239. doi: 10.1016/j.atherosclerosis.2011.03.016.
18. Kööbi T, Kähönen M, Iivainen T, Turjanmaa V. Simultaneous non-invasive assessment of arterial stiffness and haemodynamics—a validation study. *Clin Physiol Funct Imaging*. 2003;23:31–36.
19. Koivistoinen T, Kööbi T, Jula A, Hutri-Kähönen N, Raitakari OT, Majahalme S, Kukkonen-Harjula K, Lehtimäki T, Reunanen A, Viikari J, Turjanmaa V, Nieminen T, Kähönen M. Pulse wave velocity reference values in healthy adults aged 26-75 years. *Clin Physiol Funct Imaging*. 2007;27:191–196. doi: 10.1111/j.1475-097X.2007.00734.x.
20. Tahvanainen A, Koskela J, Tikkakoski A, Lahtela J, Leskinen M, Kähönen M, Nieminen T, Kööbi T, Mustonen J, Pörsti I. Analysis of cardiovascular responses to passive head-up tilt using continuous pulse wave analysis and impedance cardiography. *Scand J Clin Lab Invest*. 2009;69:128–137. doi: 10.1080/00365510802439098.
21. Wilenius M, Tikkakoski AJ, Tahvanainen AM, Haring A, Koskela J, Huhtala H, Kähönen M, Kööbi T, Mustonen JT, Pörsti IH. Central wave reflection is associated with peripheral arterial resistance in addition to arterial stiffness in subjects without antihypertensive medication. *BMC Cardiovasc Disord*. 2016;16:131. doi: 10.1186/s12872-016-0303-6.
22. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172; discussion 207. doi: 10.1002/sim.2929.
23. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. *Ann Intern Med*. 2009;150:795–802.
24. Pickering JW, Endre ZH. New metrics for assessing diagnostic potential of candidate biomarkers. *Clin J Am Soc Nephrol*. 2012;7:1355–1364. doi: 10.2215/CJN.09590911.
25. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, Heiss G. Arterial stiffness and the development of hypertension. The ARIC study. *Hypertension*. 1999;34:201–206.
26. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. *Hypertension*. 2005;45:426–431. doi: 10.1161/01.HYP.0000157818.58878.93.
27. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol*. 2007;50:1–13. doi: 10.1016/j.jacc.2006.12.050.
28. Pencina MJ, D'Agostino RB, Pencina KM, Janssens AC, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176:473–481. doi: 10.1093/aje/kws207.
29. Bowman TS, Gaziano JM, Buring JE, Sesso HD. A prospective study of cigarette smoking and risk of incident hypertension in women. *J Am Coll Cardiol*. 2007;50:2085–2092. doi: 10.1016/j.jacc.2007.08.017.
30. Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension*. 2007;49:981–985. doi: 10.1161/HYPERTENSIONAHA.107.087338.
31. Parati G, Salvi P. Arterial stiffness and the sympathetic nervous system. In: Safar ME, O'Rourke M, Frohlich ED, eds. *Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases*. London, UK: Springer-Verlag; 2014:163–173.

Novelty and Significance

What Is New?

- We studied the ability of pulse wave velocity to predict the progression of blood pressure and the onset of hypertension among young adults.

What Is Relevant?

- Pulse wave velocity measured 4 years earlier was a strong independent predictor of blood pressure increase and the development of hypertension.
- Pulse wave velocity improved the hypertension risk prediction beyond traditional cardiovascular risk factors.

Summary

Pulse wave velocity predicts the increase in blood pressure and development of hypertension among young adults. In addition, pulse wave velocity improves hypertension risk prediction.

Hypertension
Journal of the American Heart Association

Pulse Wave Velocity Predicts the Progression of Blood Pressure and Development of Hypertension in Young Adults

Teemu Koivistoinen, Leo-Pekka Lyytikäinen, Heikki Aatola, Tiina Luukkaala, Markus Juonala, Jorma Viikari, Terho Lehtimäki, Olli T. Raitakari, Mika Kähönen and Nina Hutri-Kähönen

Hypertension. published online January 8, 2018;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Pulse Wave Velocity Predicts the Progression of Blood Pressure and Development of Hypertension in Young Adults

Online Supplement

Teemu Koivistoinen, MD, PhD, DSc; Leo-Pekka Lyytikäinen, MD; Heikki Aatola, MD, PhD; Tiina Luukkaala, MSc; Markus Juonala, MD, PhD; Jorma Viikari, MD, PhD; Terho Lehtimäki, MD, PhD; Olli T. Raitakari, MD, PhD; Mika Kähönen, MD, PhD; Nina Hutri-Kähönen, MD, PhD.

Corresponding author

Teemu Koivistoinen

Tampere University Hospital, Department of Clinical Physiology

P.O. Box 2000, FI-33521 Tampere, FINLAND

E-mail: teemu.koivistoinen@outlook.com

Tel. +358 3 31165394; fax. +358 3 3116 5511

Table S1. Associations of risk factors measured in 2007 with blood pressure measured in 2011.

Systolic blood pressure measured in 2011					
Whole population (n=1449)			**Subpopulation (n=1183)**		
Variables measured in 2007	**β±SE**	**P value**	**Variables measured in 2007**	**β±SE**	**P value**
Systolic blood pressure	7.69±0.44	<0.001	Systolic blood pressure	5.52±0.40	<0.001
Initiation of antihypertensive medication	-5.18±1.48	<0.001	PWV	2.80±0.33	<0.001
PWV	3.01±0.33	<0.001	Sex	1.86±0.71	0.010
BMI	1.15±0.36	0.001	Smoking	1.79±0.75	0.016
Diastolic blood pressure	-1.07±0.42	0.011	BMI	1.46±0.36	<0.001
Insulin	0.72±0.36	0.043	Heart rate	0.68±0.30	0.025
Age	0.23±0.06	<0.001	Age	0.23±0.06	<0.001

Diastolic blood pressure measured in 2011					
Whole population (n=1449)			**Subpopulation (n=1183)**		
Variables measured in 2007	**β±SE**	**P value**	**Variables measured in 2007**	**β±SE**	**P value**
Diastolic blood pressure	3.61±0.32	<0.001	Diastolic blood pressure	2.60±0.29	<0.001
Initiation of antihypertensive medication	-2.85±1.13	0.012	PWV	2.12±0.25	<0.001
PWV	2.31±0.25	<0.001	Sex	1.94±0.55	<0.001
Sex	1.82±0.51	<0.001	BMI	1.33±0.28	<0.001
BMI	1.01±0.27	<0.001	Heart rate	0.72±0.23	0.002
Systolic blood pressure	0.88±0.34	0.009	Age	0.15±0.05	0.001
Glucose	-0.73±0.23	0.002			
Heart rate	0.57±0.22	0.010			
Age	0.13±0.04	0.003			

Multivariable models included sex and age, HDL cholesterol, LDL cholesterol, triglycerides, glucose, insulin, body mass index (BMI), smoking, C-reactive protein, heart rate, systolic and

diastolic blood pressure, and pulse wave velocity (PWV) measured in 2007. In addition, models included initiation of antihypertensive medication between 2007 and 2011 (dichotomous variable). Variables with a statistically significant association with blood pressure are reported.

All continuous predictive variables, expect age, were standardized before regression analysis. Regression coefficient β indicates the change in systolic or diastolic blood pressure measured in 2011 when a variable measured in 2007 changed by 1 standard deviation (SD). For sex, smoking, and initiation of antihypertensive medication, β indicates the change in systolic or diastolic blood pressure measured in 2011 when category changed. SE: standard error. Subpopulation: subjects normotensive in 2007.

Table S2. Relationship between variables measured in 2007 and hypertension in 2011.

	Hypertension in 2011	
Variables measured in 2007	**OR (95 % CI)**	**P value**
PWV	2.16 (1.72 - 2.75)	<0.001
Systolic blood pressure	1.89 (1.43 - 2.51)	<0.001
Smoking	1.64 (0.94 - 2.81)	0.077
BMI	1.36 (1.08 - 1.72)	0.008

The multivariable model included sex and age, as well as HDL cholesterol, LDL cholesterol, triglycerides, glucose, insulin, body mass index, smoking, C-reactive protein, heart rate, systolic and diastolic blood pressure, and pulse wave velocity (PWV) measured in 2007. Variables with a statistically significant or borderline significant ($p<0.08$) association with hypertension are reported. Analyses performed on 679 subjects who were normotensive in 2007. 153 (22.5%) of these subjects had hypertension in 2011.

Hypertension was defined as systolic blood pressure ≥ 120 mmHg, diastolic blood pressure ≥ 80 mmHg, self-reported use of antihypertensive medication, or self-reported hypertension diagnosis.

OR: odds ratio per 1 SD increase in predictor variable, except for smoking per change in category (nonsmoker/smoker). CI: confidence interval.

Table S3. Comparison of models for the prediction of incident hypertension

Model	AUC	95 % CI	P value	NRI events (%)	P value	NRI non-events (%)	P value	NRI total (%)	P value
Reference model	0.712	0.667-0.758	-	-	-	-	-	-	-
Reference model + PWV	0.773	0.733-0.814	<0.001	25.5	0.001	28.9	<0.001	54.4	<0.001

Reference model: age, sex, smoking, systolic and diastolic blood pressure, body mass index, LDL cholesterol, HDL cholesterol, triglycerides, glucose, insulin, heart rate, and C-reactive protein measured in 2007.

Hypertension was defined as systolic blood pressure ≥ 120 mmHg, diastolic blood pressure ≥ 80 mmHg, self-reported use of antihypertensive medication, or self-reported hypertension diagnosis.

PWV: pulse wave velocity. AUC: area under the receiver operating characteristic curve. CI: confidence interval. NRI: continuous net reclassification improvement. Event: incident hypertension.