Comparison of pulse wave velocity measured with different devices and the concept of integrated central blood pressure- aortic stiffness risk categories

PhD thesis

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1. Introduction

Given that cardiovascular (CV) diseases are still the leading causes of mortality worldwide and that an armamentarium of effective preventive medications is available, it is of utmost importance to accurately predict CV risk in different populations to increase the health benefits of CV prevention.

Arterial stiffening is a major component of vascular ageing. Measurement of arterial stiffness and central hemodynamic parameters are candidates that may improve CV risk prediction over and above classical tools. Pulse wave velocity (PWV), the most accepted biomarker of arterial stiffening can be measured by different methods and in the past decade its 24-hour monitoring has also become available.

Central systolic blood pressure (cSBP) reflecting on pressure; central pulse pressure (cPP) reflecting on pulsatility; and augmentation index (Aix) reflecting on wave reflection are also important markers of central hemodynamic properties.

Almost all validation studies with different devices are cross-sectional and compare office measurements. Comparative studies are warranted with office and 24-hour devices and also evaluating the difference in the changes of different parameters for interventions e.g., lifestyle changes or administration of antihypertensive medications.

Although most available literature on arterial stiffness investigates the predictive power of stiffness parameters individually, given that PWV, cSBP, cPP and Aix can be obtained with most available devices at a single measurement, and that they reflect different aspects of the vasculature, it seems reasonable to combine their results into a single score to predict CV outcome.

2. Objectives

The aims of our study were:

(1) to compare office and ambulatory PWVs with two devices in cross-sectional design: office cfPWV measured with the tonometric PulsePen device (PP PWV) and 1st hour and 24-hour ambulatory oscillometric PWVs evaluated with Mobil-O-Graph (Study 1);
(2) to compare the changes of PWVs in a proportion of patients after the initiation of lifestyle modifications (in white-coat hypertensive patients) or of antihypertensive medication (in hypertensive patients) (Study 1);
(3) to develop an integrated central blood pressure-aortic stiffness (ICPS) risk score and risk categories which incorporate the predictive potential of identical parameters – to predict cardiovascular events in CKD patients on conservative therapy (Study 2);
(4) study the predictive power of ICPS risk categories on CV mortality in end-stage renal disease (ESRD) patients on hemodialysis therapy, following the methodology of Study 2 (3) (Study 3).

3. Methods

3.1. Study 1

It was a cross-sectional and prospective study. Between February 2015 - March 2019 105 Caucasian individuals were recruited from one general practitioner's praxis in Budapest, Hungary. Convenience sampling was used with consecutive inclusion of those patients, whom ABPM was clinically indicated. Patients with atrial fibrillation were excluded. ABPM was required in different indications: diagnosis of newly recognized hypertension (HT) (n=35); suspect of white-coat hypertension (WhHT) (n=35); suspect of masked hypertension (n=7); control of antihypertensive therapy in chronic hypertensive patients (n=16); confirmation of resistant hypertension (n=12), or in the prospective part evaluation of the efficacy of antihypertensive therapy 3 months after medical

initiation in HT patients or evaluation of WhHT patients 12 months after the recommended lifestyle changes.

Office blood pressure was measured with a validated oscillometric device (Omron M3), office carotid-femoral pulse wave velocity (cfPWV) was evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy, PP PWV). Ambulatory blood pressure data, 1st hour (MOB 1st hour PWV) and 24-hour ambulatory pulse wave velocity (MOB 24h PWV) were evaluated by the Mobil-O-Graph NG device (I.E.M. GmbH, Germany).

3.2. Study 2 and Study 3

Both were retrospective cohort studies.

In Study 2 one hundred chronic kidney disease patients on conservative therapy (CKD 1-5) were included from 2 tertiary care nephrology outpatient clinics in Budapest, Hungary.

Patients were followed for a median of 67.6 months (interquartile range: 38.4-82.6) between April 2007 - June 2014. Follow-up was censored at the last occurrence of a documented CV event (acute coronary syndrome, heart failure requiring hospitalization, stroke or transient ischemic attack or peripheral artery disease with the need for an intervention) or death due to the above CV causes.

In Study 3 91 patients were included among ambulatory, chronic (>3 months on hemodialysis) end-stage renal disease patients of two hemodialysis units of a dialysis network, in Budapest, Hungary.

Patients were followed for a median of 29.5 months (interquartile range: 1-51). Follow-up data were collected between March 2005 and June 2009. Outcome measure was death from a CV event, which was defined as documented myocardial infarction, stroke, heart failure, malignant arrythmia leading to death or sudden cardiac death.

Patients with atrial fibrillation or with frequent ventricular extrasystoles counteracting with pulse wave analysis were excluded from both studies.
Office brachial blood pressure measurements were taken with a validated BpTru device (VSM Medtech, Vancouver, Canada). Carotid-femoral PWV and central hemodynamic parameters were measured with tonometric method, using the PulsePen device (DiaTecne, Milan, Italy).

PWV, cSBP, cPP and Aix were measured. A score was assigned to tertiles based on each parameter's ability to individually predict cardiovascular outcome. The sum of these scores and three ICPS risk categories as predictors were studied. Finally, we compared discrimination of the ICPS risk categories with PWV, cSBP and cPP.

4. Results

4.1 Study1: Cross-sectional comparison of office and ambulatory pulse wave velocity by two methods, and their changes after lifestyle or medical interventions in hypertension

4.1.1. Cross-sectional comparison of PulsePen and Mobil-O-Graph PWV

In the whole population PP PWV was higher than MOB 1st hour PWV (difference: 1.2 (-0.5-2.6) m/s, $p<0.001$) and MOB 24h PWV (difference: 1.3 (0.3-2.2) m/s, $p<0.001$).

Baseline PP PWV and MOB 1st hour PWV did not correlate with each other ($r=0.095$, $p=0.339$), but significant correlation was found between PP PWV and MOB 24h PWV ($r=0.723$, $p<0.001$). Correlation was assessed using Pearson's correlation coefficient.

PWV readings of the two devices were analyzed according to the method proposed by Bland and Altman. The Bland-Altman analysis of PP PWV with MOB 1st hour PWV and MOB 24h PWV indicate that the 95% limits of agreement

between the two methods ranged from -4.36 to 6.96 and -2.01 to 4.83, respectively.

4.1.2. Comparison of hypertensive and white-coat hypertensive patients' PWV changes during follow-up

Both office and 24-hour systolic and diastolic blood pressures decreased significantly in HT patients for the effect of therapy. After lifestyle changes, in WhHT patients' office systolic blood pressure also decreased in the 12-month control. PP PWV significantly decreased both in HT (with 0.9 (0.4-1.5) m/s, $p<0.05$) and WhHT patients (with 0.3 (-0.1-1) m/s, $p<0.05$). MOB 1st hour PWV did not change significantly neither in HT, nor in WhHT. MOB 24h PWV decreased only in HT patients (with 0.2 (0-0.6) m/s) while an increasing tendency appeared in WhHT patients. Compared with MOB 24h PWV, PP PWV decreased in significantly higher amount both in HT and WhHT patients ($p=0.01$ and $p=0.028$, respectively). Compared with MOB 1st hour PWV, PP PWV decreased in significantly higher amount only in HT patients ($p=0.032$).

4.1.3. Determinants of the three examined PWVs

Univariate and multivariate linear regression analyses were performed to analyze the determinants of PP PWV, MOB 1st hour and MOB 24h PWV in baseline and in the prospective part of the study after the follow-up as well. In univariate analyses PP PWV was significantly associated with age and office brachial systolic blood pressure. MOB 1st hour PWV was significantly associated also with brachial systolic blood pressure and with heart rate, while MOB 24h PWV was significantly and very strongly associated with age and also with diabetes, smoking, 24-hour diastolic blood pressure and 24-hour heart rate.

In multivariate analyses, age, sex, traditional cardiovascular risk factors (smoking, BMI, LDL), diabetes and

hemodynamic parameters (office brachial SBP, office brachial DBP, office heart rate) were involved into the calculations. The variability of PP PWV was determined in 57.5% with the included confounders. MOB 1st hour PWV variability was determined in much lower degree (13.3%). In contrast, MOB 24h PWV variability was almost completely determined by the included confounders (96.8%).

Finally, univariate regression analyses were also performed between 1st hour and 24-hour systolic blood pressure changes, between different blood pressure changes and PP and MOB 24h PWV changes and also between PP and MOB 24h PWV changes. We found only a tendency of significance in the changes of office SBP and 24-hour SBP (adjusted R^2= 0.03, p=0.130). There was a significant association between the drop of office SBP and PP PWV decrease (adjusted R^2= 0.140, p= 0.010), and we found a robust association between 24-hour SBP change and MOB 24h PWV change (adjusted R^2= 0.952, p<0.001) and also a significant association between PP PWV and MOB 24h PWV change (adjusted R^2= 0.196, p= 0.002).

4.2 Study 2: Integrated central blood pressure–aortic stiffness (ICPS) risk score for cardiovascular risk stratification in chronic kidney disease

Of the 108 patients eligible for inclusion 5 individuals declined participation. Further 3 patients were excluded because of missing baseline or follow-up data, leaving 100 subjects in the analytical sample.

During follow-up, 49 CV events were recorded: 16 patients died from CV causes (acute coronary syndrome n=4, stroke n=3, heart failure n=8, and peripheral artery disease n=1), and there were 33 additional non-fatal CV events (acute coronary syndrome n=8, stroke n=6, heart failure n=12, and peripheral artery disease n=7).

The relationship between parameters and cardiovascular outcome were studied in two models. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, brachial systolic blood pressure, LDL-cholesterol, current smoking, diabetes, body mass index, known cardiovascular disease and eGFR.

First, we looked at the association between the one standard deviation change in the parameters and the cardiovascular mortality with Cox regression analysis. All the four studied parameters were significantly related to CV outcomes in Model 1. In the further adjusted Model 2, the association of PWV and cPP was attenuated to non-significance, while cSBP and Aix showed significant associations.

Next, patients were divided into tertiles based on their PWV, cSBP, cPP and Aix values, respectively. Survival was investigated using Kaplan-Meier analysis and Cox-regressions. According to these results, Aix was not related to CV outcome and was excluded from further analysis. There was a linear association between PWV and cPP and CV outcomes, and accordingly 0, 1 and 2 points were given to the consecutive tertiles. As the risk of CV events or CV mortality only increased in the third tertile of cSBP, 0 points were given to the first two tertiles and 1 point to the third.

	1st tertile	2nd tertile	3rd tertile
PWV	-	1 point	2 points
c)P	-	1 point	2 points
cSBP	-	-	1 point
Aix	-	-	-

The integrated central blood pressure- aortic stiffness (ICPS) score was calculated for each patient by summing the points based on tertiles (range: 0-5 points). Survival was investigated with Kaplan-Meier and Cox regression analyses (Model 1) with ICPS score as the predictor and CV event or CV mortality as outcome (**Figure 1A**). Given the limited statistical

power of our relatively small sample size, patients were classified into three ICPS risk categories: average (0-2 points), high (3-4 points) or very high (5 points). The predictive role of these risk categories was investigated in Kaplan-Meier curves and Cox regressions (**Figure 1B**).

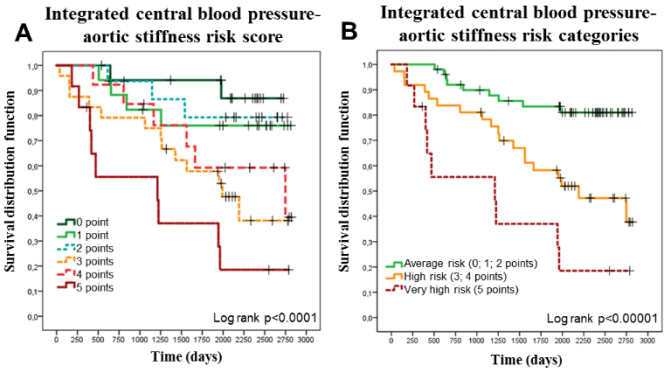

Figure 1. Kaplan–Meier survival curves for the integrated central blood pressure–aortic stiffness (ICPS) risk scores and ICPS risk categories for cardiovascular events (CV mortality and CV events) as outcomes in Study 2. Adjusted for age and sex. **Panel A**: ICPS risk score groups; **Panel B**: ICPS risk categories.

Using average risk group as reference, in Model 1, patients in high and very high ICPS risk categories had increased cardiovascular risk. High and very high ICPS risk categories remained independent predictors in Model 2 adjusted for multiple CV risk factors (**Table 1**).

Finally, the ICPS risk categories and one SD change of each of its components (PWV, cSBP and cPP) were analyzed in the same Cox-regression model for CV outcomes. To investigate model discrimination, Harrell's concordance statistics were utilized (**Table 2**). ICPS risk categories showed better discrimination than PWV and cSBP and there has been a tendency of significance in case of cPP.

	N	Hazard ratio	95% CI		P-value
ICPS risk categories					
Model 1					
Average	51	1 (ref.)			
High	37	3.517	1.650	7.494	**0.001**
Very high	12	7.559	3.201	17.850	**<0.001**
Model 2					
Average	51	1 (ref.)			
High	37	4.583	1.867	11.253	**0.001**
Very high	12	8.563	3.086	23.758	**<0.001**
Diabetes	44	3.073	1.680	5.621	**<0.001**

Table 1. The relation of integrated central blood pressure- aortic stiffness (ICPS) risk categories with cardiovascular morbidity and mortality

Variable	Coefficient	Standard error	95% CI		P-value
ICPS risk categories	0.723	0.036	0.652	0.795	**<0.001**
PWV	0.659	0.037	0.586	0.732	**<0.001**
cSBP	0.660	0.038	0.584	0.735	**<0.001**
cPP	0.691	0.035	0.621	0.761	**<0.001**
ICPS risk categories vs PWV	0.065	0.029	0.007	0.122	**0.028**
ICPS risk categories vs cSBP	0.064	0.024	0.017	0.110	**0.008**
ICPS risk categories vs cPP	0.032	0.023	-0.014	0.079	0.170

Table 2. Comparison of the discriminative ability of the ICPS risk categories with the one standard deviation change of PWV, cSBP and cPP

4.3 Study 3: Integrated Central Blood Pressure-aortic Stiffness (ICPS) Risk Categories and Cardiovascular Mortality in End-stage Renal Disease

Altogether 126 chronic HD patients at the two dialysis units were invited to participate. Of these, 28 patients declined participation and 7 were excluded because of atrial fibrillation leaving 91 patients for the analytical sample.

During follow-up, 31 cardiovascular deaths were recorded: 7 patients died from myocardial infarction, 7 from sudden cardiac death, 3 from arrythmia, 8 from heart failure and 6 from stroke.

The relationship between parameters and cardiovascular output were studied in two models. Model 1 was unadjusted, while Model 2 was adjusted for age, sex, brachial systolic blood pressure, LDL-cholesterol, current smoking, diabetes, body mass index and history of CV disease.

We looked at the association between the one standard deviation change in the parameters and the cardiovascular mortality with Cox regression analysis. As a single independent variable, only PWV was significantly related to CV mortality.

Patients were divided into tertiles based on their PWV, cSBP, cPP and Aix values, respectively. The second tertile of PWV in Model 1 and the second and the third tertiles of cSBP in Model 2 were related to the outcome. Kaplan-Meyer curves for each tertile demonstrated non-linear associations: showing an increase in the second and third tertile of PWV and cPP and only in the third tertile of cSBP. As Aix tertiles were not related to outcome and the tertile curves crossed each other, this parameter was omitted from the ICPS score calculation.

	1st tertile	2nd tertile	3rd tertile
PWV	-	1 point	1 point
cSBP	-	-	1 point
cPP	-	1 point	1 point
Aix	-	-	-

The integrated central blood pressure- aortic stiffness (ICPS) score was calculated for each patient by summing the points based on tertiles (range: 0-3 points).

The risk categories were based on the results of the Cox-models (**Table 3**) and the Kaplan–Meier curves (**Figure 2A**) by collapsing ICPS scores with similar hazard ratios to improve statistical power (Model 1).

	N	Hazard ratio	95% CI		P-value
ICPS risk categories					
Model 1					
Average	35	1 (ref.)			
High	33	1.902	0.748	4.837	0.177
Very high	23	2.910	1.145	7.396	**0.025**
Model 2					
Average	51	1 (ref.)			
High	33	2.622	0.816	8.432	0.106
Very high	23	10.034	1.666	60.425	**0.012**

Table 3. The relation of integrated central blood pressure- aortic stiffness (ICPS) risk categories with cardiovascular morbidity and mortality

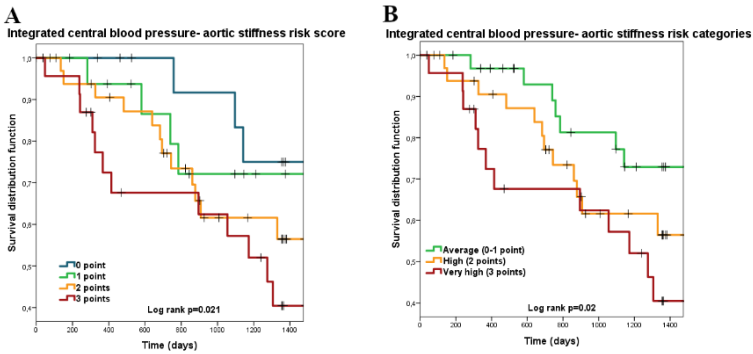

Figure 2. Kaplan–Meier survival curves for the integrated central blood pressure-aortic stiffness (ICPS) risk scores and ICPS risk categories for cardiovascular mortality as outcome in Study 3. Unadjusted. **Panel A:** ICPS risk score groups; **Panel B**: ICPS risk categories

Patients were classified into three ICPS risk categories: average (0-1 point), high (2 points) or very high (3 points). Almost two-third participants were classified into the high and very high-risk categories. Kaplan–Meier survival curves for the three ICPS risk categories are shown in **Figure 2B**. Participants in the very high ICPS risk category had a substantially increased CV mortality risk and also a stepwise increase from average through high to very high risk after adjustment for multiple CV risk factors. In Model 2, besides the very high ICPS risk category older age (HR: 1.05, 95% CI: 1.01–1.09) and lower systemic SBP (HR: 0.97, 95% CI: 0.94– 1.00) remained independent predictors of CV mortality.

Variable	**Coefficient**	**Standard error**	**95% CI**		**P-value**
ICPS risk categories	0.622	0.049	0.525	0.719	**<0.001**
PWV	0.662	0.052	0.558	0.766	**<0.001**
cSBP	0.561	0.052	0.456	0.665	**<0.001**
cPP	0.588	0.05	0.489	0.687	**<0.001**
ICPS risk categories vs PWV	-0.04	0.051	-0.142	0.062	0.438
ICPS risk categories vs cSBP	0.061	0.028	0.006	0.117	**0.031**
ICPS risk categories vs cPP	0.034	0.028	-0.022	0.089	0.226

Table 4. Comparison of the discriminative ability of the ICPS risk categories with the one standard deviation change of PWV, cSBP and cPP

Finally, to compare the predictive value of the ICPS risk categories and each of its components (PWV, cSBP and cPP),

all parameters were sequentially entered into a Cox-regression model with CV mortality as outcome. To investigate and compare discrimination of the different stiffness measures, Harrell's concordance (Harrell's C) statistics were calculated (**Table 4**). All C-values show moderate discrimination, however discrimination by ICPS risk categories was superior to that of cSBP. A tendency may also be seen in the case of cPP, while ICPS risk categories and PWV had similar C-statistics.

5. Conclusions

The main findings of our studies are the follows:

1. The tonometric PulsePen and the oscillometric Mobil-O-Graph device are not interchangeable and for 24-hour PWV values a lower threshold limit of normality should be considered.

2. The PWV response for antihypertensive therapy was more pronounced with the PulsePen device and for lifestyle changes in white-coat hypertensive patients only PP PWV decreased. Marked differences were found between the amount of contribution of determinants of different PWVs.

3. Our integrated score and the constructed ICPS risk categories provided strong and robust association with CV outcomes in CKD patients on conservative therapy (Study 2), which highlights the possible advantages of the combined measure of arterial stiffness and central hemodynamic parameters for CV risk prediction. High and very high ICPS risk categories remained independent predictors in a model adjusted for multiple CV risk factors. ICPS risk categories showed better discrimination than PWV and cSBP and there has been a tendency of significance in case of cPP.

4. Together with our previous results of CKD patients on conservative therapy, our study in ESRD patients (Study 3) is the second independent cohort where our new concept

demonstrated promising results. We found a strong gradual association between ICPS risk categories and CV outcome even after adjustment for multiple potential confounders. ICPS risk categories had a modest discrimination that was significantly better than that of cSBP. The ICPS risk categories may improve the identification of ESRD patients with high CV mortality risk.

6. Bibliography of the candidate's publications

Publications related to the thesis:

Batta D, Körösi B, Gyöngyösi H, Nemcsik-Bencze Z, László A, Tislér A, Cseprekál O, Nemcsik J. (2022) Cross-sectional comparison of office and ambulatory pulse wave velocity by two methods, and their changes after lifestyle or medical interventions in hypertension. J Hypertens, 40: 470-477. IF: 4.776

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impact factor: 0.519

∑IF: 21. 030