Pulse

Pulse 2016;4:175–179
DOI: 10.1159/000453073
Received: August 19, 2016
Accepted after revision: November 4, 2016
Published online: December 1, 2016

2235–8676/16/0044–0175$39.50/0
www.karger.com/pls

Mini-Review

Estimated Pulse Wave Velocity Calculated from Age and Mean Arterial Blood Pressure

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Keywords
Carotid-femoral pulse wave velocity · Cardiovascular risk · Predictive value

Abstract
In a recently published paper, Greve et al [J Hypertens 2016;34:1279–1289] investigate whether the estimated carotid-femoral pulse wave velocity (ePWV), calculated using an equation derived from the relationship between carotid-femoral pulse wave velocity (cfPWV), age, and blood pressure, predicts cardiovascular disease (CVD) as good as the measured cfPWV. Because ePWV predicts CVD as good as cfPWV, some might wonder whether ePWV could be replaced by cfPWV, which is a time-consuming measurement requiring an expensive apparatus. This question is addressed in this mini-review.

Background

The Reference Values for Arterial Stiffness Collaboration has published European reference values for carotid-femoral pulse wave velocity (cfPWV) together with an equation describing how cfPWV is related to age and the mean arterial blood pressure (MAP) in groups with different a priori cardiovascular (CV) risk, taking nonlinearity and interactions into account [1].

In several studies, cfPWV has been demonstrated to predict development of CV events independently of traditional risk factors in different populations [2–5]. However, although affordable and easy-to-use devices are under development, the current measurement of cfPWV requires an expensive apparatus, well-trained personnel, and extended examination time [6].

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DOI: 10.1159/000453073

In the recently published paper by Greve et al. [7], our group has demonstrated that an estimated cfPWV (ePWV) can be calculated from age and MAP using the equation from the Reference Values for Arterial Stiffness Collaborations' publication in a general Danish population of 2,366 subjects and its replication in 1,045 hypertensives from a Paris cohort.

This mini-review will address the question whether ePWV could be a good substitute for cfPWV when cfPWV is not accessible.

Discussion

Why to Calculate ePWV?

cfPWV does predict CVD in different populations independently of traditional CV risk factors [2, 3], and therefore, the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for the management of hypertension recommend measuring cfPWV as a marker of target organ damage in order to improve CV risk prediction [8]. The gold standard method for measuring cfPWV is applanation tonometry with relatively expensive devices such as the Complior system or SphygmoCor system. To ensure adequate reproducibility and correctness of measures, the personnel have to be well trained. The subject of investigation should be fasting, without caffeine intake for at least 3 h before the procedure, lying in the supine position for 10 min before a brachial blood pressure is measured and used to calibrate the device [6]. For comparative measures, the measurements should be done at the same time of the day due to diurnal variation. All these requirements make correct measurements of cfPWV outside the hospital department difficult because the price of the equipment, the need of trained personnel, and the time dedicated to the measurement make it unattractive for the general practitioner.

Because of the relative inaccessibility of high-quality applanation tonometry for measuring cfPWV, simpler methods have been developed, including the Mobil-O-Graph® system (IEM GmbH, Stolberg, Germany) [9, 10] and the Arteriograph® system (TensioMed Kft., Budapest, Hungary) [11] (both estimating aortic PWV from the oscillometric determination of the brachial artery waveform), the pOpmetre® system (Axelife SAS, Saint Nicolas de Redon, France) that measures the finger-toe transit time overlapping the aortic pathway [12], and a connected bathroom scale (Withings, Issy-les-Moulineaux, France) using ballistocardiography and impedance photoplethysmography [13].

An alternative to the use of affordable, easy-to-use systems for measuring aortic PWV is to elaborate an estimated index of aortic PWV not requiring measurement. ePWV is calculated using only age and MAP, and therefore, might be a possible alternative to cfPWV [7]. The equation from the Reference Values for Arterial Stiffness Collaboration generated comparable levels of ePWV and cfPWV, but with large individual variations.

Predictive Value of ePWV

ePWV predicted the composite CV endpoint (CEP), CV death, nonfatal myocardial infarction, nonfatal stroke and hospitalization for ischemic heart disease independently of the European SCORE risk (Systematic COronary Risk Evaluation), the Framingham Risk Score (FRS) as well as cfPWV, and added significantly to the Cox regression models in apparently healthy subjects [7]. Overall, in apparently healthy subjects, the hazard ratios for ePWV were not significantly different from those for cfPWV, and when included in the same model, both ePWV and cfPWV significantly predicted CEP. However, among patients, defined as persons with a history of CVD or diabetes and persons in treatment with antihypertensive drugs, cholesterol-reducing drugs or antidiabetic drugs, ePWV in contrast to the measured cfPWV did not have additive predictive value [7]. This suggests that ePWV and cfPWV do not catch

the same risk information. This might be due to high individual variability, or more likely to the fact that MAP, and thereby ePWV, was influenced more by antihypertensive treatment than cfPWV and prognosis.

The predictive value of the Cox regression models assessed by C-statistics was not increased by adding ePWV or cfPWV, suggesting that some of the added predictive value in cfPWV, and especially in ePWV, was included in the traditional CV risk scores, first of all in FRS. However, the C-statistics in general lacks sensitivity.

In the clinical setting, it is an important observation that ePWV predicts CEP as good as cfPWV in apparently healthy individuals in whom we need better risk classification tools and not in patients who per definition already are at a high risk and/or receiving pharmacological prevention.

Clinical Value of ePWV

The clinical value of a risk marker can be evaluated using the Net Reclassification index (NRI) [14]. A clinically successful reclassification is accomplished when a risk marker significantly more often reclassifies subjects who later experience CEP than subjects who do not, from a risk group not indicating pharmacological prevention to a risk group indicating pharmacological prevention.

In a reclassification model in which cfPWV and/or ePWV >10 m/s results in a reclassification 1 SCORE risk category up among apparently healthy subjects NRI was significant (NRI_{ePWV} = 9.5%, NRI_{cfPWV} = 7.0%, and $NRI_{ePWV+cfPWV}$ = 10.8%). However, NRI was not significant when FRS was used instead of SCORE. The higher NRI using SCORE may reflect that SCORE was constructed to predict CV death and not CEP [7]. When investigating indication for primary CV prevention, only the apparently healthy subjects are of interest. As only subjects with a moderate SCORE risk had the possibility to experience a reclassification of clinical impact (i.e. initiation of pharmacological prevention), we have also calculated NRI for subjects with a moderate SCORE risk separately, still reclassifying 1 risk category up if cfPWV and/or ePWV was > 10 m/s: NRI_{ePWV} = 11.0% (p = 0.13), NRI_{cfPWV} = 1.8% (p = 0.72), and $NRI_{ePWVcfPWV}$ = 11.6% (p = 0.21). Although insignificant, these results indicate that in our Danish population cohort of apparently healthy subjects, cfPWV carries very little additive prognostic information in subjects with a moderate SCORE risk, which is consistent with previous findings [15, 16]. In contrast, ePWV seems to add prognostic information in this clinically very relevant group of apparently healthy subjects with a moderate SCORE risk. These findings further support the hypothesis that ePWV, although correlated to cfPWV and comparable in size, does not entirely reflect cfPWV but something associated with and still different from cfPWV. More likely, the ePWV equation incorporates some complex prognostic interactions between blood pressure and age not accounted for in the traditional risk scores and not fully covered by cfPWV.

In reclassification models where subjects with ePWV and/or cfPWV >10 m/s are reclassified to a higher risk group and subjects with ePWV and/or cfPWV <10 m/s are reclassified to a lower risk category NRI is higher and more significant. However, there are some problems with this kind of reclassification where subjects are moved to either higher or lower risk categories. In subjects reclassified from a high to a very high SCORE risk or from a low to a moderate SCORE risk, there is little need to change treatment indication and there is no clinical consequence. By contrast, reclassification from a high to a moderate SCORE risk means that subjects with a traditionally high risk are moved to a risk group without indication for pharmacological prevention, which we find problematic because we have previously demonstrated that subjects with a high SCORE risk and without an elevated cfPWV still have a high risk of CV events [7, 16]. Therefore, our data rather support the use of a restricted reclassification model focusing on subjects with a moderate SCORE risk and not allowing

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Table 1. Phases of evaluation of a novel risk marker

1.	Proof of concept: do the novel risk marker levels differ between subjects with and without outcome?
2.	Prospective validation: does the novel risk marker predict the development of future outcomes in a prospective cohort or nested case-control/case-cohort study?
3.	Incremental value: does the novel marker add predictive information to established, standard risk markers?
4.	Clinical utility: does the novel risk marker change the predicted risk sufficiently to change the recommended therapy?
5.	Clinical outcome: does the use of novel risk markers improve clinical outcomes, especially when tested in a randomized clinical trial?
6.	Cost-effectiveness: does the use of the marker improve clinical outcomes sufficiently to justify additional costs of testing and treatment?

downward reclassification in subjects without an elevated ePWV and/or cfPWV. Indeed, we do not believe that the evidence is strong enough yet not to recommend primary pharmacological prevention in subjects with a high SCORE risk and a low ePWV and/or cfPWV.

ePWV: A New Risk Marker?

The American Heart Association has published a scientific statement on how to evaluate a novel risk marker considering its importance at 6 different levels (Table 1) [17].

As a risk marker, cfPWV is higher in subjects with CV outcomes than in healthy subjects, cfPWV does predict future CV events [3, 18–20], cfPWV does add prognostic information to traditional risk factors [21], cfPWV does reclassify subjects to a higher risk category, and change recommended therapy [22]. However, it is not yet clear whether reductions in cfPWV correspond to a lower CV risk independently of traditional CV risk factors, or whether cfPWV guided therapy can improve clinical outcome sufficie4four out of 6 criteria for approval of a novel risk marker suggested by the American Heart Association.

In one study on ePWV [7], ePWV also fulfilled the same 4 out of 6 criteria. However, these results have to be replicated in future studies followed by additional studies investigating phase 5 and 6 in order to evaluate the effectiveness of ePWV as a CV risk marker.

Conclusion and Perspectives

The recently published paper by Greve et al. [7] presents data suggesting prognostic and clinical value of ePWV. According to this smaller study, ePWV does predict CVD among apparently healthy subjects but not among subjects with a history of CVD or diabetes. ePWV also reclassifies apparently healthy subjects to a higher risk category and for some subjects changes the indication for primary pharmacological prevention.

It is well accepted that cfPWV is an integrated measure of the central conduit arteries' (primarily the aorta) reaction to many years of exposure to the harmful effects of CV risk factors. Although closely related to cfPWV, ePWV predicted CEP independently of traditional risk scores and cfPWV. This underlines that ePWV cannot substitute for cfPWV but implies instead that the equation by which ePWV was calculated incorporates some complex prognostic interactions between blood pressure and age not accounted for in the traditional risk scores and not fully covered by cfPWV. This hypothesis should be investigated further and, if

supported in other studies, should lead to adjustments of the traditional risk scores in order to improve their predictive value. It is also important to remember that ePWV in contrast to cfPWV only predicted CEP in apparently healthy subjects and not in subjects with history of CVD. Therefore, based on current knowledge, ePWV is not a substitute for cfPWV, but rather a prognostic addition to traditional risk scores and cfPWV in apparently healthy subjects. ePWV might be a new, easily applicable marker of elevated CV risk but not a substitution of cfPWV.

Disclosure Statement

There are no conflicts of interest to disclose.

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