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Prognostic significance of mechanical biomarkers derived from pulse wave analysis for predicting long-term cardiovascular mortality in two population-based cohorts

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ABSTRACT

Background: Numerous mechanical biomarkers derived from pulse wave analysis (PWA) have been proposed to predict cardiovascular outcomes. However, whether these biomarkers carry independent prognostic value and clinical utility beyond traditional cardiovascular risk factors hasn't been systematically evaluated. We aimed to investigate the additive utility of PWA-derived biomarkers in two independent population-based cohorts.
Methods: PWA on central arterial pressure waveforms obtained from subjects without a prior history of cardiovascular diseases of two studies was conducted based on the wave transmission and reservoir-wave theory: firstly in the Kinmen study (1272 individuals, a median follow-up of 19.8 years); and then in the Cardiovascular Disease Risk Factors Two-Township Study (2221 individuals, median follow-up of 10 years). The incremental value of the biomarkers was evaluated by net reclassification index (NRI).
Results: In multivariate Cox analyses accounting for age, gender, body mass index, systolic blood pressure, fasting glucose, high-density- and low-density-lipoprotein cholesterol, and smoking, only systolic (SC) and diastolic rate constant (DC) of reservoir pressure could independently and consistently predict cardiovascular mortality in both cohorts and the combined cohort (SC: hazard ratio 1.18 [95% confidence interval 1.08–1.28, $p < 0.001$; DC: 1.18 [1.09–1.28], $p < 0.001$]. Risk prediction estimates in traditional risk prediction models were significantly more accurate when incorporating peak of reservoir pressure (NRI = 0.049, $p = 0.0361$), SC (NRI = 0.043, $p = 0.0236$) and DC (NRI = 0.054, $p = 0.047$).
Conclusions: Of all PWA-derived biomarkers, SC and DC were consistently identified as valuable parameters for incremental cardiovascular risk prediction in two large prospective cohorts.

1. Introduction

The arterial system functions both as a conduit and as a reservoir [1]. Vascular aging and its associated arterial stiffening have a major impact on the arterial pressure waveform and cardiovascular risk. The peak and trough of arterial pressure waveforms, systolic and diastolic blood pressure (BP), have been linearly associated with the risk of cardiovascular events [2]. The Windkessel and wave transmission theories have been

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used to model the complex interactions between the heart and the arterial system, and both distinctively provide explanations on the changes in the arterial pressure waveform with aging and diseases. Based on the wave transmission theory, the arterial pressure waveform is composed of a forward wave and a reflected wave. Increased wave reflection measured by the pulse wave analysis (PWA) is related to the extent of myocardial ischemia in patients with [3] and without [4] obstructive coronary artery disease. The pressure wave reflection is also directly related to left ventricular hypertrophy [5] and its regression with treatment [6], to left atrial size [7], and is inversely related to left ventricular diastolic function at rest [7] and during exercise [8]. An increase in wave reflection has been associated with a decreased renal function [9] and with an impaired outcome following acute ischemic stroke [10]. Using a triangulation method, we were able to decompose the central pressure waveforms derived by tonometry into their forward wave amplitudes and backward wave amplitudes (Pb) and demonstrate that Pb predicts long-term cardiovascular mortality in men and women independent of arterial stiffness [11,12].

Recently, the reservoir function of vascular systems has been modeled by Wang et al. as the volume related pressure changes in arterial [13] and venous vascular systems [14]. Aortic stiffening with advancing age not only leads to an accelerated wave speed and more pronounced wave reflections [11], but also to a reduced reservoir function. Parameters based on the reservoir-wave concept that combines elements of wave transmission and Windkessel models of arterial pressure generation were shown to predict clinical outcomes in hypertensive patients in two randomized control trials, ANBP2 [15] and ASCOT-CAFÉ studies [16].

As a result, current PWA can provide parameters based on both the wave transmission theory and the reservoir-wave analysis. However, whether these biomarkers confer independent prognostic value beyond traditional cardiovascular risk factors, has not been comprehensively and systematically evaluated.

Although numerous novel biomarkers have been proposed in various study populations, reproducibility is vital to assure that previous results are reliable and valid and could be applied to new situations. Results should be repeated in studies with different subjects and experimenters. Therefore, the aim of the present study was to examine the prognostic value and the incremental clinical utilities of these PWA-derived mechanical biomarkers in two independent population based cohorts.

2. Methods

2.1. Study population

The characteristics of participants and patient enrollment process of the first cohort from Kinmen have been detailed elsewhere [17]. In brief, a previous community-based survey was conducted in 1992–1993 in Kinmen [18], from which a total of 1272 normotensive and untreated hypertensive Taiwanese subjects (47.0% women, mean age 52 ± 13 years old, range 30–79 years) were drawn after excluding participants with a previous history of diabetes mellitus, angina pectoris, peripheral vascular disease, and any clinical or echocardiographic evidence of other significant cardiac diseases. The study protocol was approved by the institutional review board at the Johns Hopkins University and Informed consent was obtained from all participants.

To demonstrate the reproducibility, the prognostic value of all PWA-derived biomarkers was then examined in the second cohort from the "Cardiovascular Disease Risk Factors Two-Township Study" (CVDFACTS), a community-based follow-up study focusing on risk factor evaluation and cardiovascular disease development in Taiwan [19,20]. Of the participants in CVDFACTS, a total of 2211 individuals without a prior history of cardiovascular diseases had undergone measurements of arterial tonometry during their cycle 4 examination (1997–1999).

2.2. Data collection

After being seated for at least 5 min, measurements of brachial systolic BP (SBP) and diastolic BP (DBP) from the right arm of subjects were manually taken with a mercury sphygmomanometer and a standard-sized cuff (13 cm × 50 cm). Reported blood pressures represent the average of at least two consecutive measurements separated by at least 5 min. Brachial pulse pressure (PP) was calculated as [brachial SBP − brachial DBP]. Overnight fasting serum and plasma samples were drawn for blood chemistry analysis.

2.3. Central arterial pulse wave analysis (Fig. 1)

In the Kinmen study, right carotid artery pressure waveforms, which have been demonstrated to closely resemble central aortic pressure waveforms [21–23], were registered noninvasively with a tonometer [18,24]. The common carotid artery pressure waveforms were calibrated with brachial mean BP (MBP) and DBP to obtain the carotid BP [21]. Recently, it has been argued that MBP should be estimated as brachial DBP along with 40% of brachial artery pulse pressure [25]. We therefore conducted a sensitivity analysis by using a brachial form factor of either 0.33 or 0.4 to evaluate the impact of different calibrating methods on the prognostic significance of these mechanical biomarkers (Appendix I). Because the prognostic value (hazard ratio and Wald Chi^2) were comparable between these two methods, we therefore only present the results of a traditional calibrating method with a form factor of 0.33. In the CVDFACTS study, central aortic pressure waveforms were obtained with a SphygmoCor device (AtCor Medical, Sydney, Australia) using radial arterial pressure waveforms and a validated generalized transfer function according to the manufacturer's instructions [26]. Radial arterial pressure waveforms, obtained by applanation tonometry using a solid-state high-fidelity external Millar transducer, were calibrated with cuff SBP and DBP values, and then mathematically transformed by the validated transfer function [26] into corresponding central aortic pressure waveforms. Central PP was calculated as central SBP − central DBP.

Digitized central arterial pressure waveform signals were analyzed using custom-designed software on a commercial software package (Matlab®, version 4.2 and 7.0, The MathWorks, Inc.). To avoid inter- and intra-observer variations, we performed a fully automatic batch analysis for all processed individual signals. The inflection point was recognized on the calibrated central arterial pressure waveform using the zero-crossing timings of the fourth derivative of the pressure wave [27]. Augmentation index (AI) was calculated accordingly [23]. Forward and reflected components of the central arterial pressure waveform were separated using the triangulation method based on the following equations [28]:

$$Pf(t) = [Pm(t) + Zc \times F(t)]/2$$
$$Pb(t) = [Pm(t) - Zc \times F(t)]/2$$

where Pm(t) is the central arterial pressure wave, F(t) is the approximated triangular-shaped flow wave, Zc is the characteristic impedance, Pf(t) is the forward pressure wave, and Pb(t) is the backward pressure component. Pf and Pb are the pressure amplitudes of Pf(t) and Pb(t), respectively. The accuracy of the triangulation method in obtaining the magnitude of Pf and Pb has been validated previously [11,28]. Reflection magnitude (RM) was calculated as Pb / Pf.

2.4. Reservoir-wave analysis

Reservoir-wave analysis is a time-domain analysis, based on the understanding that the arterial system not only functions as a conduit system, conducting waves to periphery, but also as a hydraulic integrator, by which the arterial system charges during systole as inflow exceeding outflow, and discharges during diastole, through recoiling of the elastic