Manuscript Proposal #2550

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1. a. Full Title:
Utility of Heart-Carotid Pulse Wave Velocity in a Population Based Cohort

   b. Abbreviated Title (Length 26 characters): Heart-Carotid Pulse Wave Velocity

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. O.B. [please confirm with your initials electronically or in writing]

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3. Timeline:
Analysis to start immediately; Manuscript to be written and sent for publication within one year of approval

4. Rationale:
Pulse wave velocity (PWV) is the best established index of arterial stiffness [1]. Increased PWV has been associated with atherosclerosis risk factors including hypertension [2], diabetes mellitus [3] and dyslipidemia [4], and end organ injury including end-stage kidney disease [5,6]. PWV can be determined simultaneously through several arterial segments such as the heart-carotid (hc), heart-brachial (hb), heart-femoral (hf), heart-ankle (ha), carotid-brachial (cb) brachial-ankle (ba) and femoral-ankle (fa) segments.

Vascular dynamics differ along the arterial tree. In fact no single arterial segment has identical viscoelastic properties, and it is impossible to extrapolate segmental arterial properties to the whole arterial tree [1]. The aorta and its major branches (example carotid artery) are distensible, elastic with cushioning functions. These functions are achieved by absorption of left ventricular stroke volume by the large elastic vessels, with conversion of the energy received during systole into stretch of the arterial walls. The walls recoil as pressure within the vessel falls, and the stored energy is returned during diastole to maintain the blood pressure and distal blood flow during this period of the cardiac cycle. Thus, this segment “buffers” the stroke volume and is the major determinant of afterload [7]. Moreover, the proximal arteries are composed of vascular smooth muscle cells prominently involved with the secretion of extracellular matrix proteins (elastin and collagen) and are highly sensitive to age-related changes and changes in blood pressure. Decreased compliance in the large arteries induces macrovascular damage in organs such as the kidneys and the brain once the “cushion” effect that absorbs systolic pulsations is lost, causing the microvasculature to be subjected to pulsatile flow. As opposed to central arteries, peripheral arteries are less elastic and, thus, stiffer with an increasingly predominant conduit function rather than buffering function. The distal arterial compartment is mainly composed of cells with contractile properties, which are highly sensitive to endothelial vasoactive substances. [7]

Among different arterial segments, cf-PWV is currently considered as the “reference-standard” measurement of arterial stiffness. It has been used in epidemiological studies demonstrating the predictive value of aortic stiffness for CV events [1]. Its reproducibility and methodology is well established [1]. It corresponds to the widely accepted propagative model of the arterial system. However, measured along the aortic and aorto-iliac pathway, it reflects the properties of a mixed elastic and muscular part of the arterial tree. Additionally, cf-PWV does not encompass the ascending aorta, which plays the most important role in buffering and cushioning of cardiac pulsations. Moreover, the femoral pressure waveform may be difficult to record accurately in patients with metabolic syndrome, obesity, diabetes, and peripheral artery disease [1]. In the presence of aortic, iliac, or proximal femoral stenosis, the pressure wave may be attenuated and delayed. Abdominal obesity, particularly in men, and large bust size in women can make distance measurements inaccurate [1]. Finally, the measurement of path length may be prone to errors. Hence additional approaches towards measuring PWV may be of value.

Measurement of PWV at elastic arterial segments is of particular interest because of aforementioned physiological and clinical properties. Limited evidence showed that measurement of PWV of elastic arterial segments would be superior to measurement of PWV of muscular arterial segments in certain populations. Kimoto et al. compared 161 patients with type 2 diabetes and 129 healthy age and sex matched subjects who underwent measurement of hc-PWV, hb-PWV, hf-PWV and fa-PWV. The effect of diabetes on PWV was greater in the
proximal elastic segments (hc-PWV, hf-PWV) than segments with mix muscular-elastic properties (hb-PWV, fa-PWV) segments [8]. Tsuchikura et al. demonstrated that as compared to the subjects without atherosclerotic disease, those with CAD, CVD, or PAD showed higher measurements of PWV measured in various arterial segments but the levels were particularly higher for arterial segments with predominantly elastic properties [9]. In a study of 434 patients with type 2 diabetes, the PWV in elastic-predominant arterial segments was more predictive of development of chronic kidney disease than in muscular-predominant and mixed arterial segments [10]. Kim et al. investigated the association of diabetic retinopathy and PWV measurements in different arterial segments and hfPWV but not haPWV, hcPWV and baPWV was significantly associated with diabetic retinopathy [11].

Heart-carotid PWV (hc-PWV) is of particular interest to this research study given that it is a central arterial PWV measurement with aforementioned physiological and clinical implications as well as its practicality. Also given proximity to heart, it can provide non invasive, indirect assessment of left ventricular physiological parameters. Its value has not been evaluated in a large cohort study and we propose to do so in the ARIC study.

5. Main Hypothesis/Study Questions:
Main hypothesis: HC-PWV can be reliably used in a community based cohort and it will show stronger association with cardiovascular risk factors than does cf-PWV.

Study Aims:
  a. To assess reliability of hc-PWV.
  b. To assess the association between hc-PWV and cf-PWV
  c. To assess the determinants of hc-PWV (ie. Cardiovascular risk factors) and test the strength of associations with the cardiovascular risk factors and compare the strength of association with cf-PWV
  d. To assess the association of hc-PWV with conventional cardiac parameters of structure and function such as LV mass, LV wall thickness, E/e’ ratio

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

Study Design, Inclusion/exclusion:

Study design: The proposed study will be a cross-sectional study design using data acquired from all ARIC study centers on visit 5.

Inclusions: Participants in ARIC visit 5 who have PWV measures available will be included in the analysis.

Exclusions: Standard ARIC exclusions (race exclusions for different communities) will apply. Subjects will also be excluded for missing information on PWV, blood pressure, and antihypertensive medication use or other covariates of interest; and for exclusions recommended
by the ARIC ABI/PWV Working group: participants with BMI > 40 kg/m², participants with major arrhythmias (based on ECG data), reported use of antiarrhythmic or vasoactive medications per the ARIC medication survey use (MSR Item 33.g) and/or specific medication codes in the ARIC database.

Summary of data analysis:
Participant characteristics and cardiac parameters will be reported as means and standard deviations, as medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. If lack of normality is not a concern and transformation is not required then conventional statistics will be used. For non-normal data, transformations and/or non-parametric testing will be used. Chi-square analyses will be used for comparison of categorical variables and analysis of variance (ANOVA) will be used for continuous variables. Correlation coefficients will be described to test the correlation between the two PWV measurements. In addition cumulative frequency distributions, graphic displays and quantile (percentile) regression will be pursued to identify the relationship between the 2 PWV measures. Finally reclassification tables based on classifying the 2 PWV measures quartiles will be pursued to identify how similar or different the 2 PWV measures are. To identify the association of cardiovascular risk factors (age, HTN, DM, total and HDL-cholesterol, systolic and diastolic BP, pulse pressure and smoking), and, cardiac parameters of structure and function as obtained on echocardiogram (left ventricular mass [indexed to BSA], left ventricular end-diastolic dimension, left atrial volume [indexed to BSA], E/e’) with each PWV, we will first describe the univariate association between the variable and the PWV measure using spline fits/percentile regression to understand the nature of the association. Then if appropriate regression analysis will be pursued to further identify the predictors of each PWV as the dependent variable.

Limitations:
Some PWV measures are missing due to technical errors, participant factors, and scheduling conflicts. Some echo measures have missing values due to inadequate image quality or participant or technical factors.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes   ___X__ No

   b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _____ Yes   _____ No

8.a. Will the DNA data be used in this manuscript? _____ Yes   ___X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? _____ Yes   _____ No

9. The lead author of this manuscript proposal has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.

   _____ Yes   ___X__ No
References


