Heart, Lung and Circulation (2016) **25,** 855–861
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2016.01.019

ORIGINAL ARTICLE

Inter-arm Blood Pressure Difference and its Relationship with Retinal Microvascular Calibres in Young Individuals: The African-PREDICT Study

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Received 20 October 2015; received in revised form 22 January 2016; accepted 26 January 2016; online published-ahead-of-print 3 March 2016

Background Bilateral systolic blood pressure (SBP) differences > 10 mmHg is a common finding in clinical practice. Such BP differences in older individuals are associated with peripheral vascular disease, linked to microvascular dysfunction. Investigating retinal vessel calibres could provide insight into systemic microvascular function and may predict cardiovascular outcomes. Therefore we investigated the link between inter-arm systolic blood pressure differences (IASBPD) and the retinal microvasculature to determine the usefulness of IASBPD as an early marker of microvascular changes.

Methods In this cross-sectional study, we used data from 403 apparently healthy participants (20-30 years) (42% men; 49% black) taking part in the African-PREDICT study. Participants underwent retinal vessel imaging, anthropometric measurements and blood sampling. Brachial BP was measured sequentially in both arms to determine the mean IASBPD.

Results Participants were stratified into two groups with an IASBPD < 10 mmHg (n=329) and ≥ 10 mmHg (n=47), the only difference in characteristics being a higher right arm SBP in the latter group (p=0.005). We found no association between IASBPD and retinal vessel calibres in any group. Less than 2% of the variance in IASBPD was explained by potential risk factors, with only SBP associating independently with IASBPD (β=115; p=0.039).

Conclusion In a young population an increased IASBPD is not related to retinal vessel diameters suggesting that it does not reflect early microvascular alterations.

Keywords Inflammation • Inter-arm systolic blood pressure difference • Microvascular alterations • Peripheral vascular disease • Retinal vessel calibres • Young

Introduction

A wide range of differences in brachial systolic blood pressure (SBP) are often observed between arms in clinical practice [1,2]. The National Institute of Health and Clinical Excellence (NICE) considers an inter-arm systolic blood pressure difference (IASBPD) smaller that 10 mmHg as normal [3]. In contrast an IASBPD greater than 10 mmHg is regarded as clinically significant [1] and increases the risk for cardiovascular disease (CVD) [4]. It was suggested that an IASBPD is prompted by a pathological rather than physiological cause [2]. A greater IASBPD is thus more common in

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the elderly [5] and those with pathology [2,6–10] during which alterations in the structure and function of the vasculature occurs [11]. However, an IASBPD is not uncommon in young, healthy individuals [12].

Inter-arm systolic blood pressure differences have mostly been studied in diseased patients, including those with diabetes [6], metabolic syndrome [10], ischaemic stroke [9], coronary artery disease [7] and chronic kidney disease [8]. In the context of this present study IASBPD was associated with hypertension [13,14], and peripheral vascular disease (PVD) [2,6,15,16] as well as arterial stiffness [17] and might reflect endothelial dysfunction [17]. Endothelial dysfunction [18] as well as IASBPD [19] have been linked to elevated C-reactive protein (CRP) levels, a potential predictor of an increased risk for PVD [20]. Peripheral vascular disease in itself is associated with systemic microvascular dysfunction [21].

The retinal microvasculature provides a non-invasive opportunity to obtain insight into the state of the systemic microcirculation [22,23]. Abnormalities in the retinal microvasculature are predicative of CVD and mortality [24]. Respectively the retinal arteriolar and venular calibre exhibit different prognostic information [25]. Retinal arteriolar narrowing is linked to hypertension [23] whereas venular widening correlates with systemic inflammation and atherosclerotic markers [23,25–27].

Both, IASBPD [2,6,15–17,19,28] and retinal venular widening [23,25] are associated with PVD, endothelial dysfunction and inflammatory markers, whereas hypertension is associated with IASBPD [13,14] and retinal arterial narrowing [23]. It can be hypothesised that IASBPD should link positively with retinal venular widening and negatively with retinal arterial narrowing. We therefore aimed to determine whether an association exists between IASBPD and retinal vessel calibres in young individuals. Should we find a link between IASBPD and retinal vessel calibres in a young population, it may be indicative of early vascular ageing and that IASBPD may be a useful marker of early microvasculature changes.

Methods

Study Design and Subject Selection

The African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension (African-PREDICT) is an ongoing prospective study in South Africa that will recruit 1200 black and white, men and women (20-30 years of age) and perform follow-up measurements for 10-20 years. The African-PREDICT study was approved by the Health Research Ethics Committee of the North-West University (NWU-00001-12-A1). Procedures were explained to participants in their preferred language, after which all participants gave informed consent. All procedures were performed according to the Declaration of Helsinki. Participants were considered for inclusion provided that they were normotensive, HIV uninfected, not previously diagnosed with chronic disease nor using medication for chronic disease. For the purpose of this sub-study, data from the first 403 participants of the African-PREDICT study was analysed cross-sectionally.

Blood Pressure Measurement

Measurement of the brachial BP was conducted using the Dinamap Procare 100 Vital Signs Monitor (GE Medical Systems, Milwaukee, USA) with appropriately sized cuffs. Prior to the measurement being performed, participants were requested to not have smoked, exercised or eaten. They were in a seated resting state with the arm supported at heart level. The first measurement was taken on the left arm after the participant was seated calmly for $\geq$ 5 minutes. Thereafter BP was taken on the right arm in duplicate. A final measurement was made on the left upper-arm. Systolic blood pressure, diastolic BP and heart-rate were captured for each measurement.

The IASBPD was calculated by determining the mean left SBP, and the mean right SBP, and then subtracting the right arm's values from the values obtained from the left arm.

Determining Retinal Vessel Calibres

Before retinal images were taken, the participants' risk for acute anterior chamber angle glaucoma was determined with a small light source by a trained registered nurse. Participants were in a non-fasting state and were requested to refrain from food, drinks, exercise or smoking for one hour prior to the measurement. Mydriatic conditions were achieved by administering an eye drop (Tropicamide 1% from Alcon (Alcon Laboratories, Bryanston, South Africa)) into the eye, 30 minutes before the measurement. Retinal photography was performed predominantly on the right eye using a Zeiss Fundus Camera FF-450 Plus (Imedos Systems UG, Jena, Germany). Fundus images centred on the optic disc were taken using Visualis 2.81 software with the camera at a set angle of 50°. We collected monochrome and colour images. Analyses were performed using VesselMap2 software (Imedos Systems UG, Jena, Germany). All first order vessels within 0.5 – 1.0 optic disc diameters from the outer margin of the optic disc were selected as either arteriole or venule. The software automatically delineates the vessel margins. All vessel calibres were processed via the Knudtson Big 6 formula [29] and information regarding the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) were obtained. Both CRAE and CRVE were measured in measuring units (MU) where 1MU is equivalent to 1 µM if the dimensions of the eye are similar to the normal Gullstrand eye. The arteriolar-to-venular ratio (AVR) was calculated as the ratio of CRAE/CRVE. All analyses were performed by two trained researchers working in unison. The reproducibility of this method has been demonstrated in another cohort [30].

Anthropometric Measurements

Anthropometrists used standard procedures to obtain height (SECA 213 Portable Stadiometer (SECA, Hamburg,