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Different associations between beta-blockers and other antihypertensive medication combinations with brachial blood pressure and aortic waveform parameters

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ABSTRACT

Background: Comparing the relationships of antihypertensive medications with brachial blood pressure (BP) and aortic waveform parameters may help clinicians to predict the effect on the latter in brachial BP-based antihypertensive therapy. We aimed to make such comparisons with new waveform measures and a wider range of antihypertensive regimens than examined previously.
Methods: Cross-sectional analysis of 2933 adults (61% male; aged 50–84 years): 1637 on antihypertensive treatment and 1296 untreated hypertensives. Sixteen medicine regimens of up to 4 combinations of drugs from 6 antihypertensive classes were analysed. Aortic systolic BP, augmentation index (AIx), excess pressure integral (EPI), backward pressure amplitude (Pb), reflection index (RI) and pulse wave velocity (PWV) were calculated from aortic pressure waveforms derived from suprasystolic brachial measurement.
Results: Forest plots of single-drug class comparisons across regimens with the same number of drugs (for between 1- and 3-drug regimens) revealed that AIx, Pb, RI and/or $\log_e$(EPI) were higher (maximum difference = 5.6%, 2.2 mm Hg, 0.0192 and 0.13 $\log_e$(mm Hg·s), respectively) with the use of a beta-blocker compared with vasodilators and diuretics, despite no brachial systolic and diastolic BP differences. These differences were reduced (by 34–57%) or eliminated after adjustment for heart rate, and similar effects occurred when controlling for systolic ejection period or diastolic duration.
Conclusions: Beta-blocker effects on brachial BP may overestimate effects on aortic waveform parameters. Compared to other antihypertensives, beta-blockers have weaker associations with wave reflection measures and EPI; this is predominantly due to influences on heart rate.

1. Introduction

Antihypertensive medications are widely utilised and prevent incident cardiovascular (CV) events. While brachial blood pressure (BP) is routinely used as a target in such therapy, new technological advances have made it possible to make practical, non-invasive measurements that provide estimates of aortic pressure waveforms [1]. Aortic waveform parameters, which include aortic systolic BP (SBP), augmentation index (AIx) and pulse wave velocity (PWV), have been shown to predict CV events independently of brachial BP [2,3]. Thus, given their relationships with CV risk and their easy measurement in clinical practice, they may be useful targets in antihypertensive therapy. In support of this, large trials have found that antihypertensives have clinical benefits beyond those expected from decreases in brachial BP [4,5].

However, there are some issues associated with antihypertensive therapy based on aortic waveform parameters that appear to warrant further research. One issue is the relative efficacies of various antihypertensive polytherapies on these parameters. A few studies have compared the effectiveness on these waveform measures of two drugs used in combination [6–10] but we are not aware of any published study that has compared combinations of three or more

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antihypertensives. Further, these studies measured a limited range of parameters and drug combinations. In addition, some believe that heart rate and the diastolic filling period may account for differences between antihypertensive classes [11,12] and that ejection duration may also play a role [13], although the sizes of these contributions are largely unknown.

A second issue is the degree to which changes in brachial BP following antihypertensive therapy reflect changes in aortic waveform parameters. In other words, how well does brachial BP measurement capture effects of antihypertensives on these parameters? Knowledge of this would help clinicians to predict the effect on the latter when brachial BP is used as a target in such therapy. One body of evidence that informs such predictions is a meta-analysis of clinical trials, which showed that, relative to their effects on brachial BP, antihypertensives had differential effects on central BP and AIx [14]. Other clinical trials have shown that different antihypertensives had similar effects on brachial BP yet differential effects on other waveform parameters [10,15]. However, as this prior research measured a limited scope of parameters and drug combinations, study of a wider range of waveform parameters and antihypertensive regimens appears worthwhile.

The objectives of this paper were to: 1) compare associations that various antihypertensives (no treatment, monotherapies and polytherapies) have with BP variables (waveform parameters) and, 2) examine the contributions of heart rate, systolic ejection period (SEP) and diastolic duration to therapy-related differences in these associations. Particular attention was given to beta-blockers (βBs) as previous studies have found them to be less effective than other antihypertensives in reducing some of these parameters [7,16–18]. To build on existing research, in our analyses, we included a wider range of aortic waveform measures and antihypertensive regimens than used in previous studies.

2. Material and methods

2.1. Participants

The present study is a baseline (cross-sectional) analysis of the ViDA (Vitamin D Assessment) study, a randomised controlled trial of the health effects of vitamin D supplementation. Inclusion criteria were men and women aged 50–84 years and resident in Auckland at recruitment. Exclusion criteria included: 1) diagnosis of a terminal illness and/or in hospice care, 2) intending to leave New Zealand during the follow-up period, 3) taking vitamin D supplements (including cod liver oil) of >600 IU per day, 4) history of renal stones, hypercalcaemia, or medical conditions that can cause hypercalcaemia and 5) baseline serum calcium >2.50 mmol/L. All baseline data were collected during 2011–2012. Ethics approval was provided by the Ministry of Health Multi-region Ethics Committee. Written, informed consent was obtained from each participant. Full details have been published elsewhere [19].

2.2. Anthropometry, demographics and past medical history

All measurements were carried out by trained staff using a standardised protocol. Without shoes and in light clothing, height was measured with a stadiometer (±0.1 cm) and weight with digital scales (±0.1 kg). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Demographic and past medical history data were collected via questionnaires administered by trained interviewers. Ethnicity was defined by self-identification. Because patients may be more likely to be administered specific antihypertensives if they have diabetes or heart failure [20], and this could introduce indication bias in our analyses, we recorded these conditions at baseline. Participants were identified as having diabetes if they indicated that they had been told by a doctor that they have diabetes and were currently receiving insulin, medicines, tablets or pills as treatment. Participants were identified as having a history of heart failure if they had been told by a doctor that they have heart failure.

2.3. Medications

Records of all medicine prescriptions dispensed for participants before and after their interview dates were collected from the Ministry of Health. Such data included the medicine name, dose, daily dose, frequency and days of supply. To determine that measured waveform parameters could be influenced by prescribed medicines, these medicines must have been taken just prior to the interview. Therefore, medication use was defined as the prescription of a medication with days of supply that encompassed the interview date. Medicines were categorised into nitrates and six major antihypertensive classes: alpha blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), βBs, calcium channel blockers (CCBs) and diuretics. βBs were divided into vasodilating and non-vasodilating βBs, while diuretics were separated into thiazide(-like), loop and potassium-sparing diuretics, as these therapeutic sub-classes may have differential relationships with BP variables [21,22].

2.4. BP variables

After 15 minutes rest while sitting, BP (±1 mm Hg) was measured three times with an Omron T9P oscillometric device (Omron Healthcare, Kyoto, Japan) placed above the cubital fossa of the left arm and the mean of the two closest measurements were used for analyses. Suprasystolic oscillometry was carried out using a BP+ device (Uscom, Sydney, Australia) (formerly called a *R6.5 cardiovascular monitor*; Pulsecor, Auckland, New Zealand), with an appropriately sized cuff positioned on the left upper arm. The BP+ device has been shown to: 1) yield central systolic blood pressures that are highly correlated with those assessed by catheter measurement at the ascending aorta or aortic arch [23] and, 2) measure central systolic BP with good intratest and intertest reliability [24]. To improve the quality of the waveforms used in analyses, we decided *a priori* to exclude readings with a signal-to-noise ratio of <6 dB.

Augmentation index (AIx), an index of arterial stiffness and wave reflection [25], was calculated from the aortic pressure waveform using custom-written Matlab software (Mathworks, Natick, MA). A meta-analysis has shown AIx to be a predictor of CV events [2].

Aortic pressure was separated into reservoir and wave components using custom-written Matlab software (Mathworks, Natick, MA). Reservoir pressure was calculated from pressure measurements, as described elsewhere [26]. Excess pressure was calculated as measured pressure minus reservoir pressure [27]. The integral of the excess pressure waveforms (area under these waveforms) over the cardiac cycle was used to calculate excess pressure integral (EPI). EPI measures pressure associated with excess ventricular work and has been shown to predict CV events independently of brachial SBP [26].

Wave separation analysis was used to separate the aortic pressure waveform into forward and backward components [28]. The amplitude of backward pressure (Pb) was then calculated. Pb determined from this technique has previously been shown to be similar to values obtained using aortic flow waveforms measured by Doppler ultrasound [29]. Moreover, Pb has been shown to predict mortality [30] and CV events [31] independently of brachial BP. Reflection index (RI) was defined as Pb divided by the sum of Pb and the amplitude of the forward pressure [15,31].

PWV was calculated from the aortic pressure waveform using validated algorithms and derived PWV values have been shown to predict CV events independently of brachial BP [32,33]. PWV is a known predictor of CV events, as demonstrated in a meta-analysis [3]. The periods of time from the incisura to the start and end of the aortic waveform were taken as the SEP and diastolic duration, respectively [10].