



Relationships of vascular function with measures of ambulatory blood pressure variation



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ABSTRACT

Background: Characteristics of short-term blood pressure (BP) variation may influence cardiovascular disease risk via effects on vascular function.

Objective: In a cross-sectional study of a group of treated hypertensive and untreated largely normotensive subjects we investigated the relationships of measures of short-term BP variation with brachial artery vasodilator function.

Methods: A total of 163 treated hypertensive ($n = 91$) and untreated largely normotensive ($n = 72$) men and women were recruited from the general population. Measures of systolic and diastolic BP variation were calculated from 24 h ambulatory BP assessments and included: (i) rate of measurement-to-measurement BP variation (SBP-var and DBP-var); and (ii) day-to-night BP dip (SBP-dip and DBP dip). Endothelium-dependent vasodilation was assessed as flow-mediated dilation (FMD) and endothelium-independent vasodilation was assessed in response to glyceryl trinitrate (GTN). Relationships were explored using univariate and multivariate linear regression.

Results: The relationships of brachial artery vasodilator function with BP variation were not significantly different between treated hypertensive and untreated subjects, therefore these groups were combined for analysis. In univariate analysis, higher SBP-var ($P < 0.001$) and lower DBP-dip ($P = 0.004$) were associated with lower FMD; and higher SBP-var ($P = 0.002$) and lower SBP-dip ($P = 0.003$) and DBP-dip ($P = 0.001$) were associated with lower GTN-mediated dilation. In multivariate analysis, lower SBP-dip ($P = 0.007$) and DBP-dip ($P = 0.03$) were independently associated with lower GTN response.

Conclusions: Our results indicate that a lower day-to-night BP dip is independently associated with impaired smooth muscle cell function. Although rate of BP variation was associated with measures of endothelial and smooth muscle cell function, relationships were attenuated after accounting for age and BP.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of death globally [1]. High blood pressure (BP) is the leading risk factor for CVD and total mortality [2] and the measurement of BP provides the primary marker of individual risk. However, other characteristics of BP in addition to its absolute level may also contribute to risk. Two measures linked to increased CVD risk are a high BP variability [3–5] and a blunted day-to-night BP dip [6–8]. High

short-term BP variation [4,9–11] and blunted day-to-night BP dip [7,12–14] have also been associated with outcomes related to atherosclerosis and hypertensive end-organ damage. However, data supporting a link between vascular dysfunction and characteristics of short-term BP variation are limited [15–17].

The deterioration of vascular function is associated with the development of CVD [18]. Vascular function is influenced by both endothelial and smooth muscle cell function; change in endothelial function is an early event in the development of atherosclerosis and CVD [19,20]; and endothelial and smooth muscle cell functions are impaired with CVD [21] and its risk factors [22–24]. In addition, reduced brachial flow-mediated dilation (FMD) is associated with elevated risk for future CVD events [25].

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Hypertension appears to be causally related to the development of endothelial and smooth muscle cell dysfunction, but the mechanisms are not fully understood [23]. It is possible that short-term fluctuations in BP, even within the normotensive range, and a blunted day-to-night BP dip resulting from elevated night time BP could also contribute to the development of vascular dysfunction, independent of the level of BP.

The cross-sectional relationships of brachial artery vasodilator function, assessed using ultrasound, with measures of BP variation over 24 h were investigated in treated hypertensive and untreated largely normotensive individuals. We have also explored whether any observed relationships are independent of BP, age and other traditional CVD risk factors.

2. Methods

2.1. Participants

Volunteers were recruited from the general population of Perth, Australia using print media advertisements. They were recruited to two separate nutritional intervention studies [26,27] that recruited either treated hypertensive subjects only or a healthy group who were predominantly normotensive. Separate advertisements targeted generally healthy volunteers [27] and volunteers taking medication for hypertension [26]. For the purposes of initial analyses, all subjects taking antihypertensive medication were combined (treated hypertensive), and all subjects not taking antihypertensive medication were combined (untreated largely normotensive). The data used in this study was only the baseline (cross-sectional) data from these two studies. Treated hypertensive individuals had a previous physician diagnosis of hypertension. All hypertensive participants needed to be taking one or more antihypertensive drugs for at least 3 months prior to the study, in order to have stable BP at the time of the study. All participants had a 24 h ambulatory SBP less than 160 mm Hg. All participants were aged 35 to 75 y; had a body mass index of 19–36 kg/m² [2]; were non-diabetic; were not taking nitrate medication, the oral contraceptive or hormone replacement; had no major current or recent (<6 months) illness; and had not taken nutritional supplements or antibiotics at least 3 weeks prior to the study. Usual medication was taken as prescribed. The study was conducted from the University of Western Australia School of Medicine and Pharmacology located at Royal Perth Hospital in Western Australia. All individuals provided a written informed consent. Ethics approval was obtained from the University of Western Australia Ethics Committee and the Royal Perth Hospital Human Ethics Committee and the research was carried out in accordance with the Declaration of Helsinki of the World Medical Association.

2.2. Design

The cross-sectional relationship between measures of ambulatory BP variation and vascular function were investigated. Data on traditional CVD risk factors were also collected. Participants attended the School of Medicine and Pharmacology research unit located at Royal Perth Hospital, where all measurements were performed.

2.3. Ambulatory blood pressure and measures of variation

BP was assessed using a single 24 h ambulatory BP trace with BP measured every 20 min during the day and every 30 min at night [26,27]. Participants were instructed to continue their usual daily activities and to avoid any vigorous exercise. Measurements showing an error code or those with a pulse pressure of less than

20 mm Hg were excluded from the analysis. BP traces were considered complete if more than 80% of the recordings were valid.

The rate of variation of SBP and diastolic BP (DBP) (SBP-var and DBP-var) were calculated from the 24 h ambulatory BP traces for the whole 24 h period as well as day time (08:00–20:00) and night time (22:00–06:00) periods separately according to a previously described method [27]. Measurement-to-measurement BP variation was calculated using the slope of the change in SBP and DBP between each reading over time [27]. The slope for each data point in the recording is calculated and allocated to a particular hour. The absolute values of the slopes of each hour as well as the preceding and subsequent hour were averaged to give one value. This is a modification of the method described in detail by Zakopoulos et al. [9]. We also assessed BP variability using the SD of each individual's measurements over the 24-hr period. The SD of BP measurements during the day time (08:00–20:00) and night time (22:00–06:00) periods were also calculated. The weighted SD (SBP-wSD and DBP-wSD) was calculated according to the method of Bilo et al. [28]. The day-to-night dip in BP (SBP-dip and DBP-dip) was calculated as the difference between the mean day time and night time BP.

2.4. Vascular function: brachial artery vasodilator function

Brachial artery vasodilator function was assessed after a 12 h fast using ultrasound according to a previously validated protocol [29,30]. A single trained ultrasonographer performed all measurements. Endothelium-dependent vasodilation was assessed as response to forearm ischemic FMD and endothelium-independent vasodilation was assessed in response to glyceryl trinitrate (GTN; 400 µg sprayed sublingually). The FMD response provides a guide to nitric oxide-mediated endothelial cell function [31]. The GTN response provides a guide to changes in smooth muscle function that may affect the observed changes in FMD [32]. Analysis of scans was performed with semiautomated edge-detection software [29,30]. This automatically calculated the brachial artery diameter, corresponding to the internal diameter. This was gated to the R wave of ECG, with measurements taken at end diastole. Responses were calculated as the maximum percentage change in brachial artery diameter from baseline. The analysis was performed by an experienced observer. Reproducibility studies have previously demonstrated an intrasubject coefficient of variation of 14.7 and 17.6% for flow-mediated and glyceryl trinitrate-mediated dilation respectively [30].

2.5. Body weight, biochemistry and health history

Body weight was recorded with participants wearing light clothing and no footwear using Wedderburn digital scales (20–200 kg) (Wedderburn, Perth, Western Australia, Australia). Height was measured at baseline using a wall-mounted stadiometer. Waist circumference was measured at the top of the iliac crest. Fasting lipids were measured in serum samples, using routine laboratory methods in the PathWest Laboratory at Royal Perth Hospital, Western Australia. A questionnaire was used to gather information about age, use of medication, smoking history and physical activity. Because there were only 4 current smokers included, smoking status was defined as ever smoked (which included current and ex-smokers) or never smoked (non-smokers). Level of physical activity was classed as either inactive or active. Participants recorded their usual levels of physical activity as either: 'inactive'; 'low and irregular'; 'moderate and irregular'; 'moderate and regular'; or 'substantial and regular'. Participants describing their usual levels of physical activity as inactive or low and irregular were then classed as inactive and all other participants were classed as active.

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