Atherosclerosis 268 (2018) 108–116

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Aortic atherosclerosis is a key modulator of the prognostic value of postural blood pressure changes

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A R T I C L E I N F O

Article history:
Received 23 August 2017
Received in revised form
1 November 2017
Accepted 21 November 2017
Available online 26 November 2017

Keywords:
Diastolic blood pressure
Systolic blood pressure
Aortic atherosclerosis
Cardiovascular death
Blood pressure variability

A B S T R A C T

Background and aims: Orthostatic blood pressure decrease or increase has been related to cardiovascular events in hypertensive patients. Large blood pressure changes after orthostatic stress are associated with autonomic and neurohormonal abnormalities; aortic atherosclerosis (ATS) may also play a role.
Methods: We investigated the interaction of ATS on the prognostic value of postural blood pressure changes. In a cohort of 958 hypertensive patients with an aortography (mean ± standard deviation age 44 ± 11 years, 61% men, mean blood pressure 182/110 mmHg), blood pressure was measured after 10 min of rest in the supine position. Systolic blood pressure (SBP) was also measured in standing position, 1 min after the supine position. Blood pressure changes were calculated as supine SBP minus standing SBP and analyzed as absolute or arithmetic means. ATS was assessed using an aortography score.
Results: After 15 years of follow-up, 280 all-cause and 167 cardiovascular deaths occurred. In a multivariable Cox regression analysis adjusted for major cardiovascular risk factors and stratified according to ATS status, SBP changes were statistically associated with all-cause and cardiovascular mortality only in the presence of ATS: tertile 3 *versus* 1, 2.99 (1.37–6.49) and 4.08 (1.55–10.72) respectively, tertile 3 *versus* 2, 2.89 (1.29–6.46) and 4.82 (1.79–12.98), respectively (p for interaction: 0.003 for all-cause and 0.003 for cardiovascular mortality) for absolute changes. The hazard associated with the magnitude of SBP changes was more important than that associated with its direction.
Conclusions: The prognostic significance of postural SBP changes is markedly influenced by ATS in hypertensive patients.

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1. Introduction

Orthostatic blood pressure (BP) variations (i.e. hypotension or hypertension) are related to cardiovascular events and cognitive decline in hypertensive patients [1]. Orthostatic hypertension is associated with lacunar stroke, whereas orthostatic hypotension increases the risk of thrombotic non lacunar stroke [2]. Short-term BP variability, including orthostatic variability, is mainly dampened by the baroreflex [3], and is exaggerated by autonomic and neurohormonal abnormalities [4]. Aortic remodeling, which encompasses the two intertwined [5] (i.e. atherosclerotic and stiffening) processes, is also a major player to determine BP oscillations, particularly those arising from systole to diastole. Aortic remodeling increases the magnitude of these oscillations (i.e. pulse pressure [PP]). This effect has prognostic consequences as PP and heart rate strongly influence coronary events in hypertensive patients [6–8]. The two kinds of variability—postural and pulsatile—are associated, as demonstrated by the correlation between carotid–femoral pulse wave velocity and changes in short-term systolic BP (SBP) [9]. It is conceivable that they could act synergistically in impairing tissue perfusion, eventually leading to a poor long-term outcome. Thus, the aim of this study was to investigate the interaction between aortic atherosclerosis (ATS) and postural BP changes on outcomes. Electrocardiographic left ventricular hypertrophy (LVH), history of heart failure, and antihypertensive treatment were considered as other potential effect modifiers. We used a historical cohort of hypertensive patients with an ATS score

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https://doi.org/10.1016/j.atherosclerosis.2017.11.025
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based on aortography with documented cause-specific mortality after a long follow-up period.

2. Materials and methods

2.1. Patients

The study cohort has been described previously [10]. Briefly, the cohort included all patients who visited the Cardiology Department at Louis Pradel Hospital and had an aortography for hypertension work-up between January 1969 and December 1976 (n=1031). At study closure, six patients were lost to follow-up. Among the patients with complete follow-up, 958 had an assessment of BP, both in the supine and standing position, and were retained for the present analysis. Their outcomes were checked after a 15-year follow-up period.

Oral consent was obtained from all patients in accordance with the French regulation prevailing in the 1970s. The study was approved by the local review board and by the Commission Nationale Informatique et Liberté (CNIL). Under the French law, as mentioned in several published technical notes, in line with European directives [11], only the approval of the CNIL is required for single-center observational usual-care studies such as the one reported here. The vital status query was approved by national authorities before data extraction by the Institut National de la Statistique et des Etudes Economiques (INSEE).

2.2. Protocol

Our protocol was described previously [10]. For each patient, a form was completed collecting data on various morphometric characteristics, risk factors for cardiovascular events (smoking status, alcohol intake, salt consumption, etc.), history of cardiovascular disease, and current medication and symptoms.

Smoking status was defined as current tobacco consumption or consumption stopped within the previous 5 years. Six BP measurements were taken with a manual sphygmomanometer during a 10-min period in the supine position; BP was again measured once, 1 min after resuming the standing position. BP changes were calculated as mean supine BP minus mean standing BP and are expressed as absolute mean or arithmetic mean (in this case, a negative value indicates a BP decrease). Heart rate was measured by radial pulse palpation (taken over 30 s or 1 min) with the patient in the supine position only, just after BP measurement. A 12-lead electrocardiogram (ECG) was performed with the patient in the supine position.

An overnight fasting blood sample was drawn for hemogram and plasma chemistry (electrolytes, creatinine, glucose, and total cholesterol). Renal function was assessed using the Modification in Diet in Renal Disease (MDRD) formula.

Previous cardiovascular diseases included history of heart failure (clinical or chest X-ray findings such as dyspnea, edema, cardiomegaly, or pulmonary congestion), coronary artery disease (clinical findings such as angina pectoris, myocardial infarction, or Q wave on ECG), peripheral artery disease (walking impairment or pain at rest), and stroke (clinical findings).

Aortography was performed by puncture of the femoral artery. The Seldinger technique was used to diagnose renal artery stenosis, because Doppler imaging, computed tomography, and magnetic resonance imaging were not available before 1976. The descending thoracic and abdominal aorta was explored.

2.3. Potential effect modifiers

Signs of aortic atherosclerosis included calcifications, atherosclerotic plaque, stenosis, or aneurysms. These were initially categorized according to a four-modality atherosclerosis score (ATS_4), as follows: 0 when absent; 1 for mild atherosclerosis (few calcifications or atherosclerotic plaques); 2 for moderate atherosclerosis (numerous calcifications or atherosclerotic plaques); and 3 for severe atherosclerosis (stenosis or aneurysm). A simplified two-modality score (ATS_2) was used to compare patients without significant aortic atherosclerosis (ATS_2 0 when ATS_4 was 0 or 1) to those with significant aortic atherosclerosis (ATS_2 1 when ATS_4 was 2 or 3). LVH was defined by a Sokolow index >3.5 mV. History of heart failure was defined by clinical or chest X-ray findings such as dyspnea, edema, cardiomegaly, or pulmonary congestion. Diabetes was retrospectively defined as either a fasting glucose level ≥1.26 g/L (≥7.0 mmol/L) on two separate occasions or as a current use of antidiabetic medication. The use of an antihypertensive treatment at baseline was also considered as a potential interaction on the prognostic value of SBP changes.

2.4. Assessment of outcomes

Deaths at 15-year follow-up were obtained from the *Répertoire National d'Identification des Personnes Physiques*, a directory maintained by INSEE. Causes of death were then coded from the death certificates, as provided by INSERM SC8, according to the International Classification of Diseases, Ninth Revision. All subjects who were not officially declared dead were considered to be alive at the end of follow-up. The outcomes used in this study were all-cause death (cardiovascular and non-cardiovascular, including sudden death) and cardiovascular death (from cerebrovascular disease, myocardial infarction, or heart failure) as classified by the French national Centre d'Epidémiologie sur les Causes Médicales de Décès [12].

2.5. Statistical analyses

Continuous variables with close-to-normal distributions are summarized as means±standard deviations. Continuous variables with skewed distributions are summarized as medians with interquartile ranges. Categorical variables are expressed as counts and percentages. Thus, a nonparametric analysis of variance was used to compare continuous variables between orthostatic BP-change subgroups and chi-squared testing was used for between-group comparisons of dichotomous variables. Paired t-test and Wilcoxon rank analysis were used as appropriate to compare differences between BP values taken in the standing and supine positions.

The prognostic value of postural SBP changes was examined as three categorical variables: tertiles of absolute value (first tertile <10 mmHg, second tertile 10–18 mmHg, third tertile >18 mmHg); orthostatic SBP decrease (<0 mmHg) and orthostatic SBP increase (≥0 mmHg); and tertiles of arithmetic value (first tertile > −5 mmHg, second tertile −6 to −17 mmHg, third tertile < −17 mmHg). DBP changes were analyzed with three similar categorical variables: tertiles of absolute value (first tertile <5 mmHg, second tertile 5–10 mmHg, third tertile >10 mmHg); orthostatic DBP decrease (<0 mmHg) and orthostatic DBP increase (≥0 mmHg); and tertiles of arithmetic value (first tertile > −1 mmHg, second tertile −1 to −9 mmHg, third tertile < −9 mmHg).

All-cause and cardiovascular deaths were estimated by Kaplan–Meier survival curves (log–rank statistic), and by univariate and multivariable Cox regression models (Chi-squared statistic adjusted for age, sex, SBP, heart rate, diabetes, total cholesterol, smoking status, previous cardiovascular diseases, body mass index, and estimated glomerular filtration rate). The proportional hazards

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