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Association of various blood pressure variables and vascular phenotypes with coronary, stroke and renal deaths: Potential implications for prevention

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ABSTRACT

The relationship between blood pressure (BP) and cardiovascular diseases has been extensively documented. However, the benefit of anti-hypertensive drugs differs according to the type of cardiovascular event. Aortic stiffness is tightly intertwined with BP and aorta cross-talk with small arteries. We endeavored to elucidate which BP component and type of vessel remodeling was predictive of the following outcomes: fatal myocardial infarction (MI), fatal stroke, renal -, coronary- or cerebrovascular-related deaths. Large vessel remodeling was estimated by an aortography-based aortic atherosclerosis score (ATS) while small vessel disease was documented by the presence of a hypertensive retinopathy.

We included 1031 subjects referred for hypertension workup and assessed outcomes 30 years later. After adjustment for major risk factors, ATS and pulse pressure (PP) were predictive of coronary events while mean BP (MBP) and retinopathy were not. On the contrary, MBP was predictive of cerebrovascular and renal related deaths while ATS and PP were not. Retinopathy was only predictive of cerebrovascular related deaths. Lastly, the aortic atherosclerosis phenotype and increased PP identified patients prone to develop fatal MI whereas the retinopathy phenotype and increased MBP identified patients at higher risk of fatal stroke.

These results illustrate the particular feature of the resistive coronary circulation comparatively to the brain and kidneys' low-resistance circulation. Our results advocate for a rational preventive strategy based on the identification of distinct clinical phenotypes. Accordingly, decreasing MBP levels could help preventing stroke in retinopathy phenotypes whereas targeting PP is possibly more efficient in preventing MI in atherosclerotic phenotypes.

1. Introduction

The relationship between blood pressure (BP) and cardiovascular disease, namely cardiac ischemic events, heart failure and stroke, has been extensively documented [1] culminating in anti-hypertensive treatment being the cornerstone of prevention. Each additional 20 mmHg systolic BP (SBP) and 10 mmHg diastolic DBP (DBP) doubles the risk of cardiovascular events [2]. Large meta-analyses have proven the benefit of BP lowering on various outcomes [3]. Hypertension is also one of the leading causes of renal failure with BP lowering shown to be efficient at preventing renal function decline [4]. There are differences however in the extent of such preventive benefits, the latter being typically less pronounced for coronary prevention than for stroke prevention [5,6]. In

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addition, certain drugs may be more efficient than others on specific outcome e.g., calcium channel blockers on stroke [3] or renin angiotensin blockers on renal deaths [4,7], suggesting that different pathophysiological mechanisms may intervene in the genesis of these diseases.

Tightly intertwined with BP, aortic stiffness is a key player in this process by conveying pulsatility to small arteries with a permanent cross talk between large and small vessels [8] while being a major determinant of central pressure waveform. Aortic stiffness is also an accepted risk marker for cardiovascular events [9–13].

Yet, the anatomical features of target organs and consequently, the characteristics of the diseases, are notably different: 1) myocardial infarction (MI) is an homogenous disease driven by plaque rupture at the level of large epicardic arteries which are in close proximity to the aorta; 2) Stroke is a polymorphic disease although, in its hypertension-specific expression, is related to small vessel disease, i.e. vessels located far from the aorta; 3) The process of renal disease is, to some extent, akin to that of brain disease while intra-renal circulation is much closer to that of the aorta than intra-cerebral circulation.

The objective of the present study was to determine the respective contributions of BP level, aortic remodeling and small vessel diseases on coronary events compared to cerebrovascular and renal-related events, considered separately. To our knowledge, this has never been performed within the same cohort. The study took advantage of an historical cohort of hypertensive patients with an aortic atherosclerosis score based on aortography [14], and a retinopathy score based on optic fundus, with documented cause-specific mortality 30 years later.

2. Methods

A complete methods description is available in online only materials.

This study cohort [14] included 1031 patients who had a workup of their hypertension at Louis Pradel Hospital (1969–1976). Their outcomes were controlled after thirty-years of follow-up. Oral consent was obtained for every patient according to French regulations prevailing in the seventies and the study received approval of the Commission Nationale Informatique et Libertés (CNIL).

A specifically-designed form was filled out for every patient and included morphometric characteristics, cardiovascular risk factors, history of cardiovascular disease and current medication and symptoms. Peripheral BP was measured with a manual sphygmomanometer after a 10-min rest period in supine position. Systolic BP (SBP) and Diastolic BP (DBP) were each determined as the average of six measurements. As the present study aimed at identifying the pressure and the vascular contributions to the diseases, mean peripheral BP (MBP) = [SBP + 2DBP]/3 and peripheral pulse pressure (PP) = [SBP − DBP] were deemed to identify respectively the steady-state component of pressure – a rather "pure" indicator of pressure level *per se* - and the pulsatile pressure component known to be closely related to stiffness. An overnight fasting blood sample was drawn for hemogram and plasma chemistry analysis. Renal function was assessed by the Modification in Diet in Renal Disease (MDRD) formula. An optic fundus was available for all of the patients.

Aortography was performed by puncture of the femoral artery. The descending thoracic and abdominal aorta was explored. Signs of aortic atherosclerosis included calcifications, atherosclerotic plaque, stenosis or aneurysms were examined. These were initially categorized according to the severity of atherosclerosis using a 3-modality score variable (ATS): 0 when atherosclerosis was undetectable (ATS 0), 1 for mild atherosclerosis (ATS 1), 2 for moderate or severe atherosclerosis (ATS 2).

An ophtalmoscopic fundus examination was performed to assess hypertensive retinopathy using the four-grade classification of Keith, Wagener, and Barker [15].

Patients were not individually followed by our team. Outcome were assessed and classified by consulting the Institut National d'Etudes Economiques (INSEE) mortality records and the death certificates provided by INSERM SC8, following the International Classification of Diseases, Ninth Revision (ICD-9).

2.1. Statistical analysis

Continuous variables with close-to-normal distributions are expressed as means ± standard deviations. Continuous variables with skewed distributions are expressed as medians (interquartile ranges). Categorical variables are expressed as percentages. Thus, the non-parametric Kruskal Wallis test was used to compare continuous variables between ATS or retinopathy subgroups and χ^2 testing was used for between-group comparisons of dichotomous variables.

Unadjusted hazard ratios were assessed with Cox regression model for PP, MBP, ATS, and retinopathy. Adjusted hazard ratios for MBP and ATS (model 1), PP and ATS (model 2), MBP and retinopathy (model 3), PP and retinopathy (model 4) were calculated in multivariable forced Cox regression models (χ^2 statistic adjusted for age, sex, diabetes, smoking status, previous cardiovascular disease, body mass index (BMI), antihypertensive treatment and estimated glomerular filtration rate). The same models were used for fatal MI, fatal stroke and renal-related mortalities in the first analysis and then for coronary and cerebrovascular related deaths thereafter. Kaplan–Mayer curves were used to assess the predictive value of 2 vascular phenotypes i.e. (atherosclerotic or retinopathy phenotypes), in order to identify potential relevant clinical features that may help risk stratification.

The analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, USA). A P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics according to ATS or retinopathy scores

Patient demographics are summarized in Table 1. Nearly half of patients received at least one antihypertensive treatment at baseline: thiazide diuretics (37%), centrally acting drugs (32%), anti-aldosterone (15%) and beta-blockers (2%). The risk profile of patients rose with increasing ATS score. In addition, the more the calcifications, the higher the PP and MBP levels. Similarly, the risk profile markedly increased with the presence of retinopathy (Table S1).

3.2. Relationship of outcomes with pressure, ATS and retinopathy scores

During the 30-year follow-up period, 90 fatal MI were documented, 80 fatal strokes, 77 renal related deaths, 129 coronary related deaths, and 100 cerebrovascular deaths. All pressures and vascular variables of interest were associated with each outcome (Tables S2 and S3). Most other classical risk factors were also found associated with outcomes (data not shown).

Multivariable analyses are shown in Table 2 and S4. ATS was strongly associated with fatal MI and with coronary related deaths whereas it was not associated with fatal stroke or cerebrovascular related deaths. A marginal association was found with renal related deaths. PP showed the very same associations as ATS with coronary outcomes but not with cerebrovascular ones. This effect was