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Central hemodynamic modifications in diabetes mellitus☆

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ABSTRACT

Arterial stiffness in hypertension is markedly influenced by age, mean arterial pressure (MAP) and heart rate, whereas factors influencing this parameter in diabetes mellitus are not yet fully understood. The aim of our study was to compare central hemodynamics in diabetics ($n = 126$) versus non-diabetic controls ($n = 203$), most of whom were hypertensive, and with similar MAP. Anthropometric, laboratory and clinical measurements were collected. Hemodynamic parameters (central blood pressure, aortic pulse wave velocity [PWV], augmentation index [AIx] and pulse pressure amplification [PPA]) were measured using applanation tonometry. PWV and AIx were significantly higher in diabetics, after adjustment for age, gender, MAP, and heart rate. After further adjustment for metabolic syndrome, only the difference in PWV persisted ($P < 0.0001$). PPA was marginally altered though not significantly. In diabetics, PWV did not correlate with MAP, suggesting that other structural alterations, resulting from insulin resistance, may account for diabetic arterial stiffening to a greater extent than, and independently of, blood pressure. Chronic treatment with insulin was associated with increased PWV, independently of blood pressure, diabetes control and duration, or other common confounding variables. In conclusion, hypertensive diabetics had greater arterial stiffness than hypertensive controls. In diabetes, multiple factors affect arterial stiffening independently of hemodynamic status. Notably, insulin therapy (IT) is associated with more severe arterial stiffness, suggesting a consistent relationship between these parameters. It remains to be determined whether IT should be considered as a marker of diabetes severity that leads to increased arterial stiffness, or whether it has a direct/indirect effect on arterial wall modifications.

1. Introduction

Diabetes mellitus (DM) is an established cardiovascular risk (CVR) factor, affecting several million people worldwide. Metabolic factors, glycation products, endothelial dysfunction, and inflammation are possible contributors to the pathogenesis of DM-induced cardiovascular diseases (CVD) [1]. These changes affect functional/structural properties of the arterial tree that are strictly correlated with CVR. To date, CVR assessment in DM has been mainly based on measurements of peripheral systolic blood pressure (SBP) and pulse pressure (PP) [2,3]. However, recent population trials have shown central blood pressure (BP) to be superior to peripheral BP for the assessment of CVR [4], and aortic stiffness has become a recognized CVR marker [5]. These central hemodynamic parameters can be studied non-invasively using arterial applanation tonometry, to estimate central BP, aortic pulse wave velocity (PWV), a marker of aortic stiffness, augmentation index (AIx), linked to both cardiac contribution and wave reflection phenomena, and PP amplification (PPA), which implicates both aortic stiffness and wave reflection.

In the literature, diabetic subjects are often only compared to healthy controls, and changes in central hemodynamics have been reported in diabetic patients who have increased central BP and

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PWV compared to control populations [6,7]. Patients presenting with both diabetes and hypertension tend to have greater aortic stiffness than those with either disease alone [8,9], although few studies have compared diabetics and hypertensive patients with similar blood pressure levels [10]. Furthermore, few data are available about the effect of DM on arterial stiffness and BP modifications in hypertensive patients. The process of arterial stiffening in diabetic patients is influenced by both hemodynamic and mechanical factors. The latter are caused by matrix protein remodeling within the arterial wall, where non-enzymatic crosslinking between glucose and amino groups generates advanced-glycation-end-products (AGEs).

In the natural history of DM, insulin therapy (IT) is recommended when disease control is inadequate, such as can often be observed with long-standing disease. The acute physiologic effect of insulin on large arteries is a decrease in the aortic AIx, independently of peripheral artery vasodilatation. In contrast, obesity, metabolic syndrome (MetSyn), insulin resistance, and DM show an impaired response to the insulin effect [11]. However, the effect of chronic insulin treatment on aortic PWV has not been widely investigated; whether and how endogenous hyperinsulinism and IT can affect large artery stiffness and central hemodynamics have yet to be established.

To this end, we studied the levels and determinants of PWV, AIx and PPA in diabetic versus non-diabetic individuals, most of whom were hypertensive. In addition, we focused on the role of IT in the modification of hemodynamic parameters.

2. Methods

2.1. Patients

Between November 2007 and November 2008, 450 consecutive patients were prospectively examined in the ambulatory department of cardiovascular prevention at the Hôtel-Dieu Hospital (Paris, France) to determine the presence of one or more CVR factors including high BP, smoking, dyslipidemia, DM, and/or family history of premature CVD, with or without previously identified clinical events. Subjects with secondary hypertension, atrial fibrillation, chronic renal failure, congestive heart failure, or valvular heart disease were not included. Informed consent was obtained from all participants. For the present analysis, only subjects with both central and peripheral BP recordings, as well as PWV measurements, were considered. The patients included ($n = 329$) were divided into two groups: non-diabetics ($n = 203$) and diabetics ($n = 126$). The diabetic group was subdivided into two populations: patients with ($n = 59$) and patients without ($n = 67$) insulin therapy. Patient characteristics were compared between groups.

2.2. Anthropometric measurements and clinical information

Clinical information was obtained using a patient-completed questionnaire relating to age, sex, weight, height, family and personal medical history, smoking habits, and pharmacological treatment. Smoking was defined as a history of smoking and/or current smoking. Body mass index (BMI) was calculated using the universally accepted formula. MetSyn was defined according to the NCEP criteria [12]. DM was defined as fasting glucose >7 mmol/L, or use of oral antidiabetic agents or insulin. Laboratory and supplementary clinical information was obtained during hospitalization. Hypertension was defined as office SBP > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg, measured at least three times over the previous two months, or current use of antihypertensive therapy. Brachial systolic and diastolic BPs were determined using the OMRON 705IT (HEM-759E) device [2], after at least 10 min rest in the supine position. Three consecutive BP measurements were made by a single physician and the average value was used for data analysis. Central and peripheral PPs were calculated as SBP−DBP.

2.3. Tonometric analysis

Arterial tonometry was performed using the SphygmoCor® device (AtCor Medical, Sydney, Australia) in radial, carotid and femoral arteries. Radial pressure waveform was obtained and calibrated to brachial SBP and DBP measurements (obtained with the OMRON 705IT device). Mean arterial pressure (MAP) was calculated by integrating the calibrated radial pressure wave. Central pressure was determined using a transfer function from the radial artery pressure waveform. We previously described this methodology in detail [3]. AIx was automatically calculated using the SphygmoCor software. PPA was calculated as the ratio of brachial PP over central PP [4]. Carotid−femoral (aortic) PWV was determined using the foot-to-foot method over a 10-s period of consecutive waveforms [5].

2.4. Statistical analysis

Statistical analyses were performed using the SAS software version 9.0 (SAS Institute, Cary, NC). A P value ≤ 0.05 was considered to be statistically significant. Quantitative variables were expressed as mean ± standard deviation. Weight, body mass index, total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL), plasma glucose, glycated hemoglobin, heart rate (HR), PWV, central PP, PPA, and DM duration had a non-normal distribution and are presented as a median (interquartile range). Qualitative variables are expressed as frequencies and percentages. Non-normal variables were log transformed, except for total cholesterol and DM duration, to which a square root transformation was applied.

Adjusted comparisons between diabetic and non-diabetic patients, and between insulin-treated versus non-insulin treated patients, were made using an ANCOVA test and logistic regression analysis for continuous and discrete variables, respectively. Multiple regression analyses were performed to assess PWV, AIx and PPA in the total population. Correlations between PWV and age and MAP were investigated in diabetic/non-diabetic patients and in insulin/non-insulin taking patients. Interactions between age/DM and MAP/DM, as well as age/insulin and MAP/insulin on PWV, and adjusted correlations were investigated using the general linear models procedure.

3. Results

3.1. Diabetics versus non-diabetics

Subjects included ($n = 329$) ranged in age from 19 to 94 years. Anthropometric and laboratory parameters, CVR factors and drug treatments were compared between the two groups (Table 1). There were no differences in gender distribution. The diabetic population tended to be older, with greater body weight, BMI and waist circumference than the non-diabetic population. Plasma glucose and glycated hemoglobin were higher in diabetic subjects, whereas the lipid profile, as expressed by total cholesterol, HDL and LDL cholesterol levels, but not triglycerides, was better in diabetic subjects. The proportion of hypertensive patients was slightly higher in the non-diabetic group; less individuals in this latter group were receiving treatment with statins or angiotensin blockers. Treatment with beta-blockers was equally distributed between the two groups.