Evaluation of target organ damage in arterial hypertension: which role for qualitative funduscopic examination?

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Key words:
Hypertension;
Retinal abnormalities;
Target organ damage.

Background. **The objective of this study was to compare the prevalence of quantitative markers of target organ damage, such as echocardiographically documented left ventricular hypertrophy (LVH), carotid structural changes and microalbuminuria with that of retinal abnormalities detected by qualitative funduscopic examination in a large selected population of patients with essential hypertension.**

Methods. **Eight hundred consecutive untreated (n = 232) and treated (n = 568) hypertensive patients (386 men, 414 women, mean age 52.7 ± 11.8 years) referred for the first time to our out-patient clinic were included in the study. In order to search for target organ damage, they were submitted to the following procedures: 1) amydriatic retinography, 2) 24-hour urine collection for microalbuminuria, 3) echocardiography, and 4) carotid ultrasonography. Retinal changes were evaluated according to the Keith, Wagener and Barker (KWB) classification by two physicians, who had no knowledge of the patients' characteristics. Microalbuminuria was defined as a urinary albumin excretion > 30 and < 300 mg/24 hours, LVH as a left ventricular mass index ≥ 134 g/m^2 in men and ≥ 110 g/m^2 in women; finally carotid plaque was defined as a focal thickening > 1.3 mm.**

Results. **Hypertensive retinopathy was the most frequent (KWB grade I 46%, II 32%, III-IV < 2%) marker of target organ damage, followed by carotid plaques (43%), LVH (22%, eccentric LVH was the prevalent type and was 1.8 times as frequent as the concentric one) and microalbuminuria (14%).**

Conclusions. **At variance with the markers of cardiac, macrovascular and renal damage, an extremely high prevalence of retinal abnormalities (narrowings and initial arterio-venous crossings) were found in our population. If, as suggested by the WHO/ISH guidelines, these retinal abnormalities were considered as a reliable marker of target organ damage, then almost all patients would be affected by hypertensive vascular disease. Based on this evidence it is suggested that retinal abnormalities included in funduscopic grades I and II of the KWB classification should not be considered among the criteria for the quantitative detection of target organ damage.**

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Introduction

The identification of the alterations in the cardiac and vascular structure that might precisely predict the long-term prognosis and thus lead to timely preventive measures, is of great clinical relevance in arterial hypertension[1]. Traditional markers of target organ damage, such as electrocardiographically determined left ventricular hypertrophy (LVH), proteinuria, increased serum creatinine and abnormalities of the fundus oculi have all been demonstrated to be related to increased cardiovascular mortality and morbidity[2-5]. In particular, the association between elevated blood pressure (BP) values and retinal abnormalities has been described since the second half of the XIX century[6]. With the advent of refined and quantitative methodologies aimed at detecting target organ damage and in view of the increased knowledge of the pathophysiological and clinical correlates of the fundal alterations in hypertension, the limitations of the traditional classification of retinopathy based on ophthalmoscopic examination, are increasingly apparent[7,8].

The aim of this study was to evaluate the role of funduscopic examination in detecting target organ damage and to compare it to that of other markers such as echocardiographically documented LVH, carotid structural changes and microalbuminuria in a large cohort of selected hypertensive patients.

Methods

Eight hundred and sixty-four treated and untreated hypertensive patients attending the out-patient clinic of our hypertension center during a period of 12 months lasting from April 1, 1999 through March 31, 2000 were screened.

The patients had been referred for the first time to our clinic by their general practitioners. The eligibility criteria included: 1) essential hypertension defined as a diastolic BP ≥ 90 mmHg and/or a systolic BP ≥ 140 mmHg for untreated patients, and as current treatment with antihypertensive drugs, independently of BP values, for treated patients; 2) good quality echocardiographic and carotid ultrasonographic tracings; 3) the absence of secondary hypertension, congestive heart failure, previous myocardial infarction, cardiac valve diseases, history of coronary bypass; 4) informed consent. At the initial visit, 8 untreated patients were excluded owing to low BP values (< 140/90 mmHg) and 13 patients because of mitral and aortic valve disease.

Within 1 month of the initial visit all patients underwent the following procedures in our day hospital unit: 1) clinical BP measurement, 2) blood sampling for routine chemistry examinations, 3) electrocardiography, 4) 24-hour urine collection for microalbuminuria, 5) amydriatic retinography, 6) echocardiography, and 7) carotid ultrasonography. Following the above evaluation, 43 patients were excluded because of poor quality echocardiographic or carotid ultrasonographic tracings, so that the final population of the study included 800 patients.

Blood pressure measurement. BP measurements were taken during the morning (between 10 and 12 a.m.) in the out-patient clinic by a physician with a mercury sphygmomanometer (first and fifth phases of the Korotkoff sounds taken as systolic BP and diastolic BP, respectively) after the subjects had rested for 5-10 min in the sitting position. Three measurements were taken at 1-min intervals, and the average used to define the clinical systolic and diastolic BP.

Echocardiography. M-mode, two-dimensional and Doppler echocardiographic examinations were performed with subjects in the partial left decubitus position using a commercially available instrument (ATL HDI 3000, Bothell, WA, USA) equipped with a 2.25 MHz imaging transducer. The left ventricular end-diastolic and end-systolic internal diameters (LVIDd, LVIDs), the interventricular septum thickness and the posterior wall thickness (PWT) were measured during five consecutive cycles and calculated by taking the average of values observed during two-dimensionally guided M-mode tracings in accordance with the Penn Convention[9]. The left ventricular mass was estimated using Devereux's formula and normalized by the body surface area[9]. The relative wall thickness (RWT) was calculated using the following equation: RWT = ($2 \times$ PWT)/LVIDd. LVH was defined when the left ventricular mass index was ≥ 134 g/m^2 in men and ≥ 110 g/m^2 in women[10]. Patterns of left ventricular geometry were defined according to Ganau et al.[11] criteria: 1) left ventricular concentric remodeling, when a normal left ventricular mass index was combined with a RWT ≥ 0.45; 2) concentric LVH when LVH was associated with a RWT ≥ 0.45; 3) eccentric LVH when an increased left ventricular mass was associated with a RWT < 0.45.

Carotid ultrasonography. Imaging of both extracranial carotid arteries was obtained using a high resolution linear array 10 MHz probe with the patients in the supine position and with slight hyperextension of the neck. Multiple projections were used to identify any irregularity in the vessel walls. A carotid plaque was defined as the presence of a focal thickening of the intima media complex > 1.3 mm in any segment of the arteries[12]. The end-diastolic intima-media thickness (IMT) of the posterior wall of both common carotid arteries and the lumen diameter were measured 5, 10, 15, 20 mm caudally to the bulb and the average value calculated.

The IMT was calculated, using two-dimensional longitudinal sections of the carotid artery, as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line, according to the methods of Pignoli et al.[13] and of Salonen et al.[14]. Intima-media thickening of the common carotid arteries was diagnosed in the presence of an IMT ranging from 1.0 to 1.3 mm.

Retinography. All subjects underwent a bilateral non-mydriatic retinography (Topcon TRC-NW_3). Images were captured using an analogic camera (Topcon MT-1), set in order to obtain two photographs centered on the macula[15] (Fig. 1). The images, printed on a pro-

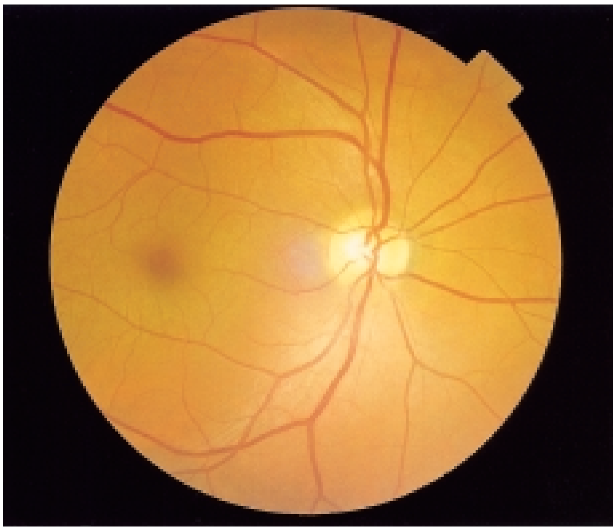

Figure 1. *Fundus oculi image obtained at amydriatic retinography.*

fessional film (Polaroid 779 High Speed Color Film ISO 640 29°) were immediately examined for quality (several photographs were taken if necessary) and were evaluated by two physicians who had no knowledge of the patients' clinical characteristics. The simplified Keith, Wagener and Barker (KWB) classification was used:
a) diffuse arteriolar narrowing: an arterio-venous ratio of at least 1:2;
b) abnormal arterio-venous crossing, any degree of depression of the vein in a crossing situated at more than one papillary diameter from the papilla;
c) retinal hemorrhages or exudates;
d) papillary edema and retinal hemorrhages and/or exudates.

The interobserver reproducibility of this technique in assessing hypertensive retinopathy was evaluated in a subgroup of 150 patients with virtually identical clinical characteristics to those of the whole population. The interobserver coefficients of variation were 25 and 31% for the assessment of diffuse arteriolar narrowing and abnormal arterio-venous crossing, respectively.

Microalbuminuria. The 24-hour urinary albumin excretion was measured using a commercially available radioimmunoassay kit (Sclavo SpA, Cinisello Balsamo-MI, Italy). The detection limit of the method was 0.5 mg/l. Microalbuminuria was defined as a urinary albumin excretion ≥ 30 and < 300 mg/24 hours.

Statistical analysis. Data are expressed as mean ± SD. Differences between the two groups were assessed using the unpaired Student's t test. Univariate relations between variables were assessed using the Pearson correlation coefficients. A two-tailed p value < 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the patients according to gender are reported in table I. Of the 800 patients included in the study, 414 (51.7%) were women and 386 men. The average age was 52.7 ± 11.8 years (range 19-89 years). With regard to other risk factors, 29% of the patients had marked hypercholesterolemia (total serum cholesterol ≥ 6.5 mmol/l), 29% were overweight (body mass index ≥ 28 kg/m^2 in men, ≥ 27 kg/m^2 in women), 21% were current smokers, 4.5% were diabetics (fasting plasma glucose ≥ 7.8 mmol/l or current antidiabetic therapy), and 4% reported previous cardiovascular events.

Echocardiographic data. One hundred and seventy-eight out of the 800 (22%) were found to have LVH as defined by echocardiographic criteria; LVH was eccentric in 113 patients and concentric in 65. The value of left ventricular mass ranged from 111 to 211 g/m^2. The prevalence of LVH was significantly higher in women than in men (p < 0.02) (Fig. 2). Concentric remodeling was detected in 143 patients (18%). Therefore 61% of all hypertensives was free of any alterations in left ventricular structure and geometry.

Carotid ultrasonographic data. Discrete carotid atherosclerosis, defined as the presence of at least one localized plaque in any segment of the arterial tree, was present in 345 patients (43%) with no statistically significant differences between men and women. Common carotid IMT was detected in 119 patients (15%) with a slight but significantly greater prevalence in men than in women. Isolated common carotid IMT (not associated with carotid plaque) was found in 9% of patients. So the overall prevalence of carotid structural alterations was 52%.

Retinal changes and microalbuminuria. A very high rate (80.5%) of retinal changes was observed. According to the KWB classification, 368 patients presented with grade I retinopathy (46%), 256 with grade II (32%), 10 with grade III (1.2%), and 2 with grade IV (0.2%). Finally, 101 patients (13%), 49 men and 52 women, were found to have microalbuminuria.

Table I. Characteristics of the study population.

	Men (n = 386)	Women (n = 414)	p
Age (years)	52 ± 12	53 ± 12	NS
Body surface area (m^2)	1.97 ± 0.2	1.67 ± 0.1	< 0.02
Clinic systolic blood pressure (mmHg)	145 ± 17	146 ± 16	NS
Clinic diastolic blood pressure (mmHg)	93 ± 9	91 ± 9	< 0.02
Heart rate (b/min)	73 ± 11	75 ± 13	< 0.03
Hypercolesterolemia (%)	23	34	< 0.001
Overweight (%)	35	25	< 0.002
Former smokers (%)	28	17	< 0.03
Current smokers (%)	24	19	NS
Diabetes (%)	6.2	2.9	< 0.02
Previous cardiovascular events (%)	5	3	NS
Current antihypertensive treatment (%)	72	71	NS

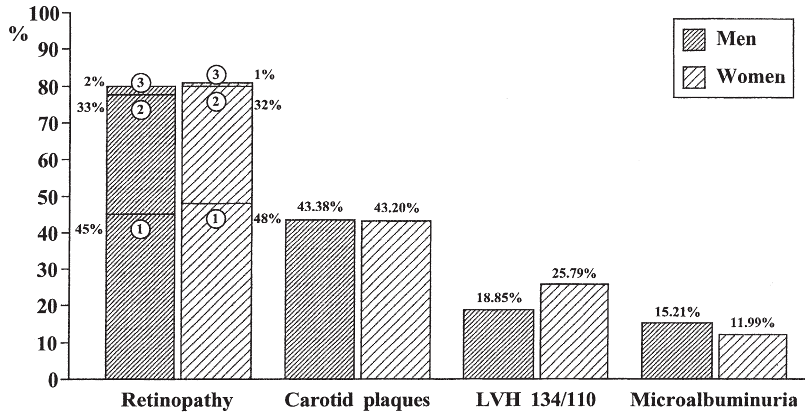

Figure 2. *Prevalence of target organ damage according to gender in 800 hypertensive patients.*

Correlations between left ventricular mass index, carotid intima-media thickness and microalbuminuria. A positive significant correlation was found between the left ventricular mass index and carotid IMT ($r = 0.41$, $p < 0.0001$), between the left ventricular mass index and microalbuminuria ($r = 0.20$, $p < 0.03$) and between carotid IMT and microalbuminuria ($r = 0.21$, $p < 0.05$) in the entire cohort of 800 hypertensive patients.

Discussion

The management of arterial hypertension should be based on the assessment of the absolute level of cardiovascular risk in each patient. According to both JNC VI and WHO/ISH recommendations[16,17], the estimation of global risk is based on BP values, coexistent modifiable and non modifiable risk factors, the presence of target organ damage and a history or clinical evidence of cardiovascular or renal disease. While precise information about the grade of hypertension, the presence of risk factors and associated diseases can be obtained by an accurate clinical history and physical examination integrated by routine investigations, detection of target organ damage for a more precise risk stratification constitutes a problematic issue. In fact, the detection of target organ damage is markedly dependent on the type of the diagnostic approach used for this purpose. In such a context, the results of our study show that the prevalence rates of preclinical complications of hypertension at the cardiac, micro and macrovascular and renal levels vary consistently (from 14 to 80%). Retinal changes were the most frequent expression of target organ damage, followed in decreasing order by carotid atherosclerosis, LVH and microalbuminuria. This marked difference in the prevalence of different signs of target organ damage in our population raises a fundamental question: which is the most sensitive and reliable marker of target organ damage in hypertensive patients? Although the examination of the fundus oculi offers a unique window for the direct observation of small arteries and arterioles, there are several reasons why the value of this diagnostic approach in uncomplicated hypertension has been put in doubt[18,19]. First, at present, thanks to the early diagnosis of hypertension and the widespread use of antihypertensive therapy, a reduced number of patients show advanced retinal vessel abnormalities. Second, the retinal tree may present age- and atherosclerosis-related structural and functional alterations that are not easily distinguishable from those induced by high BP *per se*. In this context, a major limitation of this study is the lack of information about the frequency of retinal abnormalities in a large control group of normotensive subjects with similar demographic characteristics. However, using the same technique, some years ago we found a significantly lower prevalence of initial retinal abnormalities (< 10%) in a small group of normotensive subjects compared to age-matched hypertensive patients[20]. Finally, a wide inter and intraobserver variability regarding the assessment of narrowings and crossings has been demonstrated in a number of surveys and also in the present study. Among the new quantitative markers of target organ damage, the prognostic significance of echocardiographically confirmed LVH in hypertension is well established[21,22], while that of carotid IMT or plaques and of microalbuminuria is still being investigated. LVH is widely considered as “the hemoglobin A_1C of blood pressure” since it is an objective measure of both the severity and duration of the elevation in BP[23,24]. In contrast to LVH, carotid structural changes are strongly dependent on a variety of other factors, including age, smoking, high serum cholesterol levels, and diabetes, owing to the fact that hypertension is one of the major but not the unique determinant of atherosclerosis[24]. This could explain the greater prevalence of carotid alterations (plaques and IMT) compared to LVH seen in the present and in previous studies. The main finding of this survey is the extremely high rate (80%) of retinal involvement, consisting of arterial narrowings or arterio-venous crossings in a hypertensive population with a relatively low prevalence of LVH. If considered as a proof of target organ damage, these retinal alterations would classify almost all patients in the high risk category according to the WHO-ISH classification. These data rather suggest that qualitative funduscopic examination is inadequate for an effective risk stratification of patients with mild to moderate hypertension. New techniques for the quantitative evaluation of the retinal vascular network, available in the near future, will integrate or substitute the traditional funduscopic examination for the detection of microvascular target organ damage in arterial hypertension[25-27].

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