International Journal of Cardiology 167 (2013) 1188–1192

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

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

Endothelial dysfunction predicts regression of hypertensive cardiac mass

Francesco Perticone [a,*], Raffaele Maio [a], Maria Perticone [a], Sofia Miceli [a], Angela Sciacqua [a], Eliezer J. Tassone [a], Ermal Shehaj [a], Giovanni Tripepi [b], Giorgio Sesti [a]

[a] Internal Medicine and Cardiovascular Diseases Unit, Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Italy
[b] CNR-IBIM, National Research Council, Institute of Biomedicine, Clinical Epidemiology and Physiopathology of Renal Disease and Hypertension, Reggio Calabria, Italy

ARTICLE INFO

Article history:
Received 30 December 2011
Received in revised form 4 March 2012
Accepted 14 March 2012
Available online 11 April 2012

Keywords:
Endothelial function
Left ventricular mass
Hypertension

ABSTRACT

Background: Subclinical organ damage is a condition with an increased risk for fatal and nonfatal cardiovascular events. Particularly, endothelial dysfunction and left ventricular mass (LVM) are recognized as independent predictors of cardiovascular events in hypertensive patients. Besides, LVM in hypertensives is inversely related to forearm blood flow (FBF) responses to the endothelium-dependent vasodilating agent. We evaluated the role of endothelium-dependent vasodilation in the progression/regression of LVM in a group of hypertensive subjects.

Methods: We enrolled 170 hypertensive outpatients (88 men, 92 women; age 47 ± 11 years). LVM was calculated with the Devereux formula and indexed by surface area (LVMI). Endothelium-dependent vasodilation was investigated by intra-arterial infusions of acetylcholine (ACh).

Results: During the follow-up blood pressure (BP) decreased from 150/91 ± 17/11 to 135/80 ± 14/9 mm Hg (P = 0.0001), and LVMI from 120 ± 28 to 118 ± 28 g/m^2 (P = 0.194). The mean annual rate of variation of LVMI was −0.38 ± 3.9 g/m^2, which was not statistically different in men and women. It was correlated with baseline ACh-stimulated FBF (r = −0.272, P = 0.0001) and BMI (r = 0.164, P = 0.016). At multivariate analysis, FBF was the only baseline covariate that remained significantly associated with LVMI variation, also after correction for antihypertensive treatment and BP reduction. The interaction between baseline LVM and ACh-stimulated FBF was investigated in a multiple linear regression model showing that a fixed reduction in ACh-stimulated FBF (100%) induces different variation of annual rate of LVMI at different levels of baseline LVM.

Conclusions: Our data demonstrate, for the first time, the role of endothelial function in the progression/regression of LVMI, independently of traditional cardiovascular risk factors and antihypertensive therapy.

1. Introduction

Subclinical organ damage is a condition with an increased risk for fatal and nonfatal cardiovascular events [1–6]. It is associated with essential hypertension, diabetes, dyslipidemia and other classical and emerging cardiovascular risk factors [7–10]. According with this, current guidelines recommend to recognize it to stratify global cardiovascular risk, and to choose the better pharmacological treatment to slow its progression, and to reduce both cardiovascular morbidity and mortality [10]. More recently endothelial dysfunction, the early step of the atherosclerotic process, was retained as an independent predictor of cardiovascular events in different clinical settings [4,11], new diabetes in hypertensive patients [12] and progression of both intima-media thickness [13] and estimated glomerular filtration rate decline [14].

In addition, we previously demonstrated an inverse relationship between endothelial dysfunction and hypertensive cardiac mass, hypothesizing that high blood pressure (BP) may contemporary damage different organs and/or anatomic structures [15]. On the basis of all these evidences, it is plausible to hypothesize that the endothelial activation might play a pivotal role in the appearance and progression of subclinical organ damage. In fact most of the substances produced by the activated endothelium may promote some of the inflammatory and proliferative pathways that participate to the induction of organ damage.

The increased left ventricular mass (LVM) is recognized as an independent predictor of cardiovascular events in patients with high BP [16], diabetes [17], chronic kidney disease [18], as well as in general population [1]. This is not a surprise because mechanisms involved in cardiac growth are multifactorial and interact between them. On the other hand, there are some evidences demonstrating that regression of LVM during antihypertensive treatment is associated with the reduction of cardiovascular events [19,20].

At this moment, no information exists regarding the possible influence of endothelial function on hypertensive LVM decrease.

* Corresponding author at: Department of Medical and Surgical Sciences, Campus Universitario "S. Venuta" di Germaneto, V.le Europa, 88100 Catanzaro, Italy. Tel.: +39 0961 3647149; fax: +39 0961 3647293.
E-mail address: perticone@unicz.it (F. Perticone).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2012.03.138

Therefore, we investigated, in a prospective study, the role of the baseline endothelial function, after correction for antihypertensive treatment and BP variations, in the evolution of structural cardiac mass in a group of hypertensive patients.

2. Materials and methods

2.1. Patients

We recruited 170 hypertensive outpatients (88 men and 92 women; mean age 47 ± 11 years; all white) selected from a study population previously referred to the hypertension clinic of the University Hospital of Catanzaro. At the first evaluation, patients had newly diagnosed essential hypertension with a serum creatinine < 1.5 mg/dL, without proteinuria on the dipstick test, and had never been treated previously. None of the patients had a history or clinical evidence of angina, myocardial infarction, valvular heart disease, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, or coagulopathy. Secondary forms of hypertension were excluded by a standard clinical protocol, which included measurement of plasma renin activity, aldosterone, Doppler studies of the renal arteries, and/or renal scintigraphy or renal angiography. At the first evaluation, we performed routine blood tests, assessment of atherosclerosis risk factors, evaluation of vascular function, and measurement of echocardiographic LVM. After the first evaluation, all subjects underwent standard antihypertensive treatment aimed to reduce BP < 140/90 mm Hg.

According with the aim of the study, since January 2010, patients with at least 2 years of follow-up and free of cardiovascular diseases and/or events and metabolic disorders were re-evaluated specifically cardiovascular risk factors and LVM. The local ethics committee approved the study, and all participants gave written informed consent for all procedures.

2.1.1. Echocardiograms

Tracings were taken with the patient in partial left decubitus position, using a VIVID 7 Pro ultrasound machine (GE Technologies, Milwaukee, Wisconsin, USA) with an annular phased array 2.5 MHz transducer. Echocardiographic readings were made in random order by the investigator, who had no knowledge of patients' BP and other clinical data. Only frames with optimal visualization of cardiac structures were considered for reading. The mean values from five measurements of each parameter for each patient were computed. Having the same experienced sonographer perform all studies in a dimly lit and quiet room optimized the reproducibility of measurements. In our laboratory, the intra-observer coefficient variations are 3.85% for posterior wall (PW) thickness, 3.70% for interventricular septal (IVS) thickness, 1.50% for left ventricular internal diameter (LVID) and 5.10% for LVM.

2.1.2. M-mode measurements

Tracings were recorded under two-dimensional guidance and M-mode measurements were taken at the tip of the mitral valve or just below. Measurements of IVS thickness, PW thickness and LVID were made at end-diastole and end-systole, as recommended by the American Society of Echocardiography [21]. LVM was calculated using the Devereux formula [22] and normalized by body surface area (LVMI).

Reassessment of LVMI was undertaken in all patients 92.3 ± 36.2 months later (range 28–170 months). The annual rate of reduction of LVMI (ΔLVMI per year) was determined by subtracting the LVMI value at reassessment from the LVMI at baseline and, then, dividing this value by the time interval in years between the 2 periods of evaluation for each subject.

2.2. Forearm blood flow measurement

All studies were performed at 09:00 AM after an overnight fast with the subjects lying supine in a quiet, air-conditioned room (22–24 °C). Subjects were instructed to continue their regular diet and were asked to refrain from alcohol and smoking for 24 h before the test. Forearm volume was determined by water displacement. Under local anesthesia and sterile conditions, a 20-gauge polyethylene catheter (Vasculon 2, Baxter Healthcare, Deerfield, Ill) was inserted into the brachial artery of the nondominant arm of each subject for evaluation of BP and for drug infusion. This arm was elevated slightly above the right atrium, and a mercury-filled Silastic strain gauge was placed on the widest part of the forearm. The strain gauge was connected to a plethysmograph (model EC-4, DE Hokanson, Issaquah, Wash) calibrated to measure the percent change in volume; this was connected to a chart recorder to obtain forearm blood flow (FBF) measurements. A cuff placed on the upper arm was inflated to 40 mm Hg with a rapid cuff inflator (model E-10, DE Hokanson) to exclude venous outflow from the extremity. FBF was measured as the slope of the change in forearm volume; the mean of 3 measurements was obtained at each time point.

2.3. Vascular function

We used the protocol described by Panza et al. [23] and subsequently employed by us [4,8,12,14,15]. All patients underwent measurement of FBF and BP during intra-arterial infusion of saline, acetylcholine (ACh), and sodium nitroprusside (SNP) at increasing doses. All participants rested 30 min after artery cannulation to reach a stable baseline before data collection; measurements of FBF and vascular resistance (VR) were repeated every 5 min until stable. Endothelium-dependent and -independent vasodilation were assessed by a dose–response curve to intra-arterial ACh infusions (7.5, 15, and 30 $\mu g \cdot mL^{-1} \cdot min^{-1}$, each for 5 min) and SNP infusions (0.8, 1.6, and 3.2 $\mu g \cdot mL^{-1} \cdot min^{-1}$, each for 5 min), respectively. The sequence of administration of ACh and SNP was randomized to avoid any bias related to the order of drug infusion. ACh (Sigma, Milan, Italy) was diluted with saline immediately before infusion. SNP (Malesci, Florence, Italy) was diluted in 5% glucose solution immediately before each infusion and protected from light with aluminum foil.

2.4. Statistical analysis

The analysis was performed on the complete data set, and results were expressed as mean ± SD or as percent frequency. Comparison between basal and follow-up parameters was made by unpaired Student *t* test. Successively, we divided the study population into two groups on the basis of changes in LVM from baseline to follow-up: regressors in which LVM decreases by at least 15%, and no-regressors. We considered the cut-off of 15% decrease in order to avoid a possible bias due to the intrinsic variability of cardiac mass measurements. Analysis between these two groups was made by unpaired Student *t* test, or chi-square test, as appropriate. Linear regression analysis was used to assess the relationship between baseline LVMI or annual rate of its reduction and traditional risk factors [age, body mass index (BMI), systolic BP, cholesterol, smoking status, and fasting glucose] and ACh-stimulated FBF. Finally, we constructed multivariable models using LVMI as the dependent variable. The independent predictive value of the interaction between baseline LVMI and baseline ACh-stimulated FBF for explaining the evolution of LVMI over time (dependent variable) was investigated by multiple linear regression analysis. Into the multivariate model we considered baseline LVMI, baseline ACh-stimulated FBF and their interaction term (LVMI * ACh-stimulated FBF) as well as Framingham risk factors (age, sex, smoking, systolic BP and its change during the follow-up, cholesterol, triglyceride and glucose), BMI, serum creatinine and anti-hypertensive treatment. The estimated changes in LVMI (± standard error) during the follow-up triggered by a fixed reduction in ACh-stimulated FBF (100%) across baseline values of LVMI were calculated by the standard linear combination method. In 2-tailed tests, a value of $P < 0.05$ was considered statistically significant. All calculations were made with a standard statistical package (SPSS for Windows version 12.0).

3. Results

All patients were periodically evaluated for clinical, biochemical, and cardiovascular measurements. Demographic, clinical, and humoral data of the study population at baseline and at follow-up are reported in Table 1. No significant differences were observed for BMI, smoking, total-, LDL- and HDL-cholesterol. On the contrary, a

Table 1
Baseline characteristics of the study population.

	Baseline (n = 170)	Follow-up (n = 170)	P
Age, *yrs*	47 ± 10	54 ± 12	0.0001
Gender, *M%*	88 (52)		
Body mass index, kg/m^2	27.7 ± 4.1	28.1 ± 4.5	0.377
Current smokers, *No (%)*	25 (15)	22 (13)	0.753
Total cholesterol, *mg/dL*	205 ± 33	210 ± 40	0.294
LDL-cholesterol, *mg/dL*	130 ± 35	136 ± 42	0.358
HDL-cholesterol, *mg/dL*	51 ± 12	50 ± 13	0.843
Triglyceride, *mg/dL*	118 ± 45	130 ± 59	0.036
Fasting glucose, *mg/dL*	95 ± 14	100 ± 18	0.005
Systolic BP, *mm Hg*	150 ± 17	135 ± 14	0.0001
Diastolic BP, *mm Hg*	91 ± 11	80 ± 9	0.0001
Heart rate, *bpm*	71 ± 9	73 ± 9	0.097
hs-CRP, *mg/L*	3.5 ± 1.9	3.1 ± 2.4	0.057
LVMI, g/m^2	120 ± 28	118 ± 29	0.194
Forearm blood flow			
Basal, $ml \cdot 100\ tissue^{-1} \cdot min^{-1}$	3.32 ± 0.61		
Peak, *% of increase*	344 ± 201		
Basal vascular resistance, *Units*	34.3 ± 6.8		
Antihypertensive drugs			
ACE-inhibitors		50	
Angiotensin II receptor antagonists		18	
α_1-Blockers		6	
β-Blockers		14	
Calcium channel blockers		23	
Diuretics		8	
Associations		51	