Hipertens riesgo vasc.2010;**27(1)**:27–30

Hipertensión y riesgo vascular

www.elsevier.es/hipertension

REVIEW

Evaluation of subclinical cardiac damage in arterial hypertension: From guidelines to clinical practice

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Received 14 January 2009; accepted 30 January 2009
Available online 16 de diciembre de 2009

KEYWORDS
Subclinical cardiac damage;
Echocardiography;
Electrocardiography;
Left ventricular hypertrophy

Abstract
The increased use of echocardiography and related techniques for both research and clinical purposes is related with the identification of a variety of subclinical cardiac changes in subjects with hypertension, with special relevance of left ventricular hypertrophy (LVH). LVH, assessed by electrocardiography (EKG) or echocardiography, is a strong, independent predictor for cardiovascular events and all-cause mortality in hypertensive individuals. EKG is the standard technique for detecting LVH in patients with hypertension; however, its sensitivity is lower than echocardiography. Echocardiography provides information on cardiac anatomy and function unavailable by any other means with comparable cost-effective profile and is free of any biological risk, but the technique entails a number of technical problems in imaging acquisition and data interpretation (intra- and inter-observer variability, low quality of imaging in obese subjects and in individuals with chronic pulmonary diseases, need for adequate echocardiograms. This manuscript reviews the persistent gap between clinical practice and evidence-based medicine and guidelines for subclinical cardiac damage evaluation.

PALABRAS CLAVE
Daño cardíaco subclínico,
Ecocardiografía,
Electrocardiografía,
Hipertrofía ventricular izquierda

Evaluación del daño cardíaco subclínico en la hipertensión arterial: desde las guías a la práctica clínica

Resumen
La utilización aumentada de la ecocardiografía y las técnicas relacionada tanto para los objetivos clínicos como para la investigación está relacionada con la identificación de una variedad de cambios cardíacos subclínicos en sujetos con hipertensión, con especial importancia de la hipertrofía ventricular izquierda (HVI). La HVI, evaluada por la electrocardiografía (ECG) o la ecocardiografía, es un fuerte predictor independiente para

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1889-1837/$ - see front matter
doi:10.1016/j.hipert.2009.01.006

los acontecimientos cardiovasculares y la mortalidad por todas las causas en individuos hipertensos. La ECG es una técnica estándar para la detección de la HVI en pacientes con hipertensión. Sin embargo, su sensibilidad es más baja que la de la ecocardiografía. La ecocardiografía nos proporciona información sobre la anatomía y función cardíaca que no está disponible por otros medios, con un perfil coste-efectivos comparable y está libre de cualquier riesgo biológico. Sin embargo, la técnica conlleva unos cuantos problemas técnicos en la adquisición de las imágenes y la interpretación de los datos (variabilidad intra- e inter- observador, baja calidad de las imágenes en los obesos y en individuos con enfermedades pulmonares crónicas, necesidad para ecocardiogramas adecuados. Este manuscrito revisa la laguna persistente entre la práctica clínica y la medicina basada en la evidencia con las guías para la evaluación del daño cardíaco subclínico.

Introduction

Chronic elevation in blood pressure (BP), as typically occurs in untreated or uncontrolled hypertension, may lead to progressive alterations in cardiac structure and function. Both experimental and clinical studies have shown that, in addition to pressure elevation, volume overload as well as activation of growth factors operating in essential hypertension may concur to development of left ventricular hypertrophy (LVH). LVH is generally considered a compensatory mechanism aimed at maintaining the performance of the ventricle facing an overload. However, a robust body of evidence indicate that myocardial structure in hypertensive LVH is affected by two parallel pathological processes: myocyte hypertrophy as well as a progressive accumulation of fibrous tissue within the cardiac interstitium. Thus, in hypertensive LVH a disproportionate content of cellular and non-cellular fibrous tissue occurs, accounting for the development of alterations in myocardial texture (i.e. perivascular/interstitial fibrosis and microscopic scars) and function (impaired systolic shortening, relaxation/filling and coronary reserve).[1]

In the last decades, thanks to increasing use of echocardiography and related techniques for both research and clinical purposes, a variety of subclinical cardiac changes have been described in subjects with hypertension, including LVH, systolic/diastolic dysfunction, left atrial enlargement, aortic root dilatation and myocardial fibrosis. Among this wide spectrum of cardiac alterations, most attention has been addressed to LVH, as this phenotype is relatively common and prospective data have shown that LVH, as assessed by electrocardiography (EKG) and echocardiography, is a strong, independent predictor for CV events and all-cause mortality in hypertensive individuals as well as in different clinical settings.[2–4]

A systematic search for LVH is recommended by hypertension guidelines because the identification of this damage may help to identify individuals that are particularly sensitive to the adverse effects of high BP and improve CV risk stratification over and beyond what BP levels and traditional risk factors can do.[5]

Prevalence and correlates of LVH

LVH can be detected by a variety of diagnostic methods with different sensitivity and specificity, such as EKG and ultrasound or magnetic resonance imaging. EKG is the standard technique for detecting LVH in patients with hypertension; however, its sensitivity is lower than echocardiography, as largely documented in community-based and hypertensive cohort studies in the last decades and recently confirmed by a comprehensive survey of 21 studies including more than 5000 hypertensive patients from primary to tertiary care settings.[6] The median sensitivity of the six EKG criteria tested ranged from 10.5% (range 0–39%) for the Gubner index to 21% for the Sokolow–Lyon index (range 4–52%). Taking into account these limitations, EKG should be routinely performed in all subjects with high BP in order to detect LVH, patterns of strain, ischemia and arrhythmias. In contrast, echocardiography is recommended only when a more sensitive detection of LVH is considered useful for refining CV stratification and clinical decision making (i.e. in patients in whom organ damage is not detected by routine investigations such EKG, and in the elderly in whom LVH is frequent).[5] Recent studies, assessing the prevalence of LVH determined by echocardiography and its impact on CV risk stratification in hypertensive subjects previously defined at relatively low or medium risk on the basis of routine evaluation, showed that a significant fraction of participants (up to nearly 40%) are reclassified as being at high risk after detection of LVH.[7]

Prevalence of echocardiographic LVH in the hypertensive setting is influenced by several demographic and clinical variables, such as ethnicity, age, race, gender, severity and time to exposure to BP overload, concomitant disease and risk factors (i.e. diabetes mellitus and obesity), and perhaps type of antihypertensive treatment, as well as by the partition values and indexation methods used to define LVH.[8] In uncomplicated essential hypertensives, LVH prevalence rates have been reported to range from 15% to 30% in a number of studies conducted in population-based samples and in selected patients referred to specialist centres.[9,10] Highest LVH rates (up to 70%) have been reported in patients with resistant hypertension. Studies that focused the impact of age on LVH have shown a consistent age-related increase of LV mass in both men and women. For instance, we have documented a two-fold higher prevalence of LVH in untreated hypertensive subjects 50 years of age and older compared with their younger counterparts (21.3% vs 10.1%).[11] Finally, it is worth noting that not only diagnostic thresholds but also the methods for scaling LVM to body size represent a source of variability in identifying LVH. Indexation to height$^{2.7}$, indeed, has been

shown to provide the highest LVH prevalence rates, since both obesity- and BP-related LVH are identified by this index.[12,13] In the Gubbio Population Study, a clinical survey performed in a small Italian town, LVH prevalence in a subgroup of 250 hypertensive patients was nearly two-fold higher (43.6% vs 24.0%) when LVM was indexed to height (i.e. LVMI 49.2/46.7 $g/m^{2.7}$) compared to body surface area (BSA) indexation (i.e. 116/104 g/m^2).[14]

How to assess LVH by echocardiography

An integrated echocardiographic study (including M-mode, two-dimensional and Doppler examination) may provide information about wall thickness, dimensions of LV and cardiac chambers, LV systolic and diastolic function. A proper evaluation of cardiac hypertensive involvement should also include estimation of LV mass and geometry according to validated formulae.[15] Three abnormal patterns have been described: concentric LVH (increased LV mass and relative wall thickness >0.42), eccentric LVH (increased LV mass and relative wall thickness <0.42) and concentric remodelling (normal LV mass and relative wall thickness >0.42).[6] These patterns are associated with increased incidence of cardiovascular events, and concentric LVH has consistently been proven as the highest risk phenotype.[16] The 2007 ESH/ESC guidelines suggest that detection of LVH should preferentially based on LV mass estimation, providing an indication for the criteria to be used: $>125\,g/m^2$ in men and $>110\,g/m^2$ in women.[6] Of note, this gender-specific partition value indexed to body surface area is the most common thresholds used to define cardiac hypertrophy in LVH regression studies performed in the last decade.[17] According to ESC/ESC guidelines, a report from the American Society of Echocardiography in conjunction with the European Association of Echocardiography recognizes that the sensitivity, specificity and predictive value of calculated LV mass for detection of LVH are greater than LV wall thickness measurements.[18] The inter-Society report, however, provides a number of different reference limits and partitions values of LV mass (i.e. absolute LVM, LVM/m^2, LVM/h, $LVM/h^{2.7}$), pointing out that the choice of the criteria is depending upon the population studied. For instance, in overweight and obese individuals indexation of LVM for height to allometric power of 2.7, should be more appropriate than that by BSA, although there are few data showing that a such indexation improves prediction of CV events.[19]

Diastolic dysfunction is frequently associated with LVH, since both myocyte hypertrophy and fibrosis strongly reduce passive elastic properties of the ventricle. Measurements of LV diastolic parameters have achieved a growing clinical relevance because a large proportion of heart failure may be ascribed to diastolic dysfunction. On the other hand, a variety of integrated echo-Doppler parameters derived from mitral inflow velocity, pulmonary flow velocity, colour flow-propagation velocity and more importantly myocardial velocity has improved contemporary technical capability in detecting and grading abnormal LV relaxation and filling patterns. In the Assessment of PRevalence Observational of Diastolic Dysfunction (APROS-diadys) study including 2545 elderly hypertensives (>65 years) with preserved systolic function and free of overt CV disease, diastolic dysfunction, as defined according to mitral *E/A* ratio <0.7 or >1.5, was found in 25.8% of the participants.[20] LVH was present in approximately a half of the sample, and together with systolic BP mid-wall fractional shortening was an independent covariate of diastolic dysfunction.

LVH detection in clinical practice

Although echocardiography provides information on cardiac anatomy and function unavailable by any other means with comparable cost-effective profile and is free of any biological risk, the technique entails a number of technical problems in imaging acquisition and data interpretation. Major limitations are represented by intra- and inter-observer variability (need of experienced operators), and low quality of imaging in obese subjects and in individuals with chronic pulmonary diseases. Thus, adequate echocardiograms for measurements of LV diameter and thickness cannot be obtained from all patients. Data from clinical studies in communities and selected hypertensive cohorts have shown that unsatisfactory cardiac images, limiting the chance to perform reliable quantitative measurements, range from 15% to 38%.[21] The utility of echocardiography in the management of hypertension is dependent on its accuracy in the detection of clinically important abnormalities (e.g. LVH, LV systolic and diastolic dysfunction) and, in a chronic condition like hypertension, on its ability to reliably measure serial quantitative changes during the long-term course of the disease. Therefore, these limitations should be carefully considered.

At difference from what happened only a few years ago, hypertensive patients now arrive at the clinical observation in the early phases of the disease, so that detection of marginal or mild increases in LVM prevails over more advanced LVH forms. In this scenario, diagnosis of LVH by measuring an increased LV posterior or septal wall thickness rather than LVM, may significantly underestimate subtle but clinically relevant LV structural changes. Indeed, in a study evaluating the prevalence of LVH in 92 hypertensive patients as measured by wall thickness compared to the calculation of LV mass indexed to sex-specific criteria, Leibowitz et al.[22] found that the former approach over- and underestimates LVH in males and females, respectively. In the whole study population, the accuracy of the former approach was less than 70% compared to LV mass index calculation.

Results from a pilot Italian multicentre study (confirmed by a recently concluded larger survey performed in more than 2600 patients) have pointed out that a large majority of the echocardiographic examinations routinely performed for assessing cardiac damage in hypertensive patients do not report qualifying data on LV mass, LV geometry and diastolic function.[23] Overall, these findings support the concept of a persistent gap between clinical practice and evidence-based medicine and guidelines. They also underline the need to improve the accuracy of the ultrasonographic procedures in the detection of LVH and accompanying the other alterations of cardiac phenotypes accompanying hypertension.[24]

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

The work of the two authors has been partially supported by a grant of the EC-Netwok of Excellence InGenious HyperCare (Contract no. LSHM-CT-2006–037093).

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