

Original article

Prognostic Value of Exercise-induced Left Ventricular Systolic Dysfunction in Hypertensive Patients Without Coronary Artery Disease



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ABSTRACT

Introduction and objectives: We sought to assess the prognostic value of exercise-induced left ventricular systolic dysfunction in hypertensive patients with normal resting echocardiography and absence of coronary artery disease.

Methods: From our database of patients referred for treadmill exercise echocardiography, we identified 93 hypertensive patients with preserved resting left ventricular ejection fraction ($\geq 50\%$), no evidence of structural heart disease, and absence of coronary artery disease on angiography. Overall, 39 patients developed exercise-induced left ventricular systolic dysfunction (defined as a decrease in left ventricular ejection fraction below 50% at peak exercise) and 54 exhibited a normal left ventricular ejection fraction response to exercise. The mean follow-up was 6.1 (3.7) years. End points were all-cause mortality, cardiac death, heart failure, and the composite event of cardiac death or heart failure.

Results: Patients who developed exercise-induced left ventricular systolic dysfunction were at higher risk of death from any cause (hazard ratio = 3.4; 95% confidence interval, 1.1-10.3), cardiac death (hazard ratio = 5.6; 95%CI, 1.1-29.4), heart failure (hazard ratio = 8.9; 95% confidence interval, 1.8-44.2), and the composite end point (hazard ratio = 5.7; 95% confidence interval, 1.7-19.0). In the multivariate analysis, exercise-induced left ventricular systolic dysfunction remained an independent predictor of both heart failure (hazard ratio = 6.9; 95% CI, 1.3-37.4) and the composite event of cardiac death or heart failure (hazard ratio = 4.5; 95% confidence interval, 1.2-16.0).

Conclusions: In hypertensive patients with preserved resting left ventricular ejection fraction and absence of coronary artery disease, exercise-induced left ventricular systolic dysfunction is a strong predictor of cardiac events and may represent early hypertensive heart disease.

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Valor pronóstico de la disfunción ventricular izquierda inducida por el ejercicio en pacientes hipertensos sin enfermedad arterial coronaria

RESUMEN

Introducción y objetivos: El propósito de este estudio es evaluar el valor pronóstico de la disfunción sistólica ventricular izquierda inducida por el ejercicio en pacientes hipertensos con ecocardiograma en reposo normal y sin enfermedad arterial coronaria.

Métodos: De nuestra base de datos de pacientes referidos a ecocardiografía de ejercicio, se identificó a 93 pacientes hipertensos, con fracción de eyección del ventrículo izquierdo en reposo normal ($\geq 50\%$), sin cardiopatía estructural ni evidencia de enfermedad arterial coronaria en la angiografía. Del total, 39 pacientes desarrollaron disfunción sistólica ventricular izquierda inducida por el ejercicio (definida como caída de la fracción de eyección del ventrículo izquierdo por debajo de 50% en el máximo ejercicio) y 54 mostraron una respuesta normal de la fracción de eyección del ventrículo izquierdo al ejercicio. El seguimiento medio fue 6,1 \pm 3,7 años. Los objetivos primarios fueron muerte por cualquier causa, muerte cardíaca, aparición de insuficiencia cardíaca y el evento combinado de muerte cardíaca o insuficiencia cardíaca.

Resultados: La aparición de disfunción sistólica ventricular izquierda inducida por el ejercicio se asoció con mayor riesgo de muerte por cualquier causa (hazard ratio = 3,4; intervalo de confianza del 95%, 1,1-10,3), muerte cardíaca (hazard ratio = 5,6; intervalo de confianza del 95%, 1,1-29,4),

Palabras clave:

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insuficiencia cardiaca (*hazard ratio* = 8,9; intervalo de confianza del 95%, 1,8-44,2) y del evento combinado (*hazard ratio* = 5,7; intervalo de confianza del 95%, 1,7-19,0). En un análisis multivariable, la disfunción sistólica ventricular izquierda inducida por el ejercicio continuó asociándose de manera independiente con mayor riesgo de insuficiencia cardiaca (*hazard ratio* = 6,9; intervalo de confianza del 95%, 1,3-37,4) y del evento combinado de muerte cardiaca o insuficiencia cardiaca (*hazard ratio* = 4,5; intervalo de confianza del 95%, 1,2-16,0).

Conclusiones: La aparición de disfunción sistólica ventricular izquierda inducida por el ejercicio en pacientes hipertensos con fracción de eyección del ventrículo izquierdo normal en reposo y ausencia de enfermedad arterial coronaria es un potente predictor de eventos cardiacos y podría ser un marcador precoz de cardiopatía hipertensiva.

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Abbreviations

CAD: coronary artery disease
 EILVD: exercise-induced left ventricular systolic dysfunction
 HF: heart failure
 LVEF: left ventricular ejection fraction
 LVH: left ventricular hypertrophy

INTRODUCTION

Hypertension is one of the main risk factors for the development of left ventricular hypertrophy (LVH), coronary artery disease (CAD), and heart failure (HF).¹⁻³ Patients with high blood pressure have a 2- to 3-fold risk for HF compared with normotensive subjects, as shown by data from the Framingham Heart Study.⁴ The development of hypertensive heart disease is characterized by an initial period of latent remodeling, consisting of cardiomyocyte hypertrophy, interstitial fibrosis, altered cell metabolism, and microvascular disease, among other alterations. In this regard, the time at which LVH becomes evident in echocardiography probably represents an advanced stage of myocardial damage.^{5,6} Therefore, there is a need for early detection of changes in ventricular structure and function to prevent or delay irreversible tissue injury and consequent HF onset.

Hypertensive patients with normal standard resting echocardiography may develop abnormalities of diastolic and systolic left ventricular function during exercise. Early studies demonstrated that a decrease in left ventricular ejection fraction (LVEF) may occur during exercise in patients with mild-to-moderate hypertension and absence of LVH or CAD.⁷ More recent studies have also demonstrated impaired long-axis function, and left ventricular twist and suction.⁸ All these abnormal ventricular functional changes, which are apparent only on exercise, might represent the earliest changes in hypertensive heart disease. However, the clinical implications of these findings have not been characterized so far.

The aim of this study was to assess the prognostic value of exercise-induced left ventricular systolic dysfunction (EILVD) in hypertensive patients with normal results on resting echocardiography and absence of angiographic CAD. We hypothesized that a depressed LVEF response to exercise may be an early indicator of cardiac damage identifying hypertensive patients at risk of developing HF and cardiac events.

METHODS

Patient Selection

We screened 8726 consecutive patients who underwent exercise echocardiography for clinical reasons at our institution

from November 1, 1997 to August 31, 2009. Hypertensive patients with normal resting LVEF were identified (n = 4217). Hypertension was defined as resting blood pressure > 140/90 mmHg or a previously established diagnosis. Normal resting ventricular function was considered if LVEF was ≥ 50%. We excluded patients with a history of ischemic heart disease or significant valve disease (more than mild valvular stenosis or regurgitation) and those with more than mild LVH (septal thickness or posterior wall thickness >12 mm for women and >13 mm for men).⁹ Among the remaining patients (n = 1899), we identified those who developed EILVD and who underwent a subsequent coronary angiography showing the absence of significant CAD (EILVD group; n = 39). Exercise-induced left ventricular systolic dysfunction was defined as a decrease in LVEF below 50% at peak exercise. The control group comprised 54 consecutive hypertensive patients evaluated within the same time period and with true negative exercise echocardiographic studies (ie, patients with a normal LVEF response and absence of ischemia during exercise and who underwent angiography within 3 months showing unobstructed coronary arteries). Figure 1 represents a flowchart of patients included in the study.

The demographic and clinical data and stress testing results were entered in our prospective database at the time of the procedures. All patients signed an informed consent form before testing.

Exercise Treadmill Testing

Heart rate, blood pressure, and a 12-lead resting electrocardiogram were obtained at each stage of the exercise protocol. Patients were encouraged to perform a treadmill exercise test adjusted to each patient's characteristics (Bruce protocol 90.3%; modified Bruce 6.5%, modified Bruce for sportspersons 2.2%, Naughton 1.1%) until they reached an end point. Exercise end points included physical exhaustion, significant arrhythmia, severe hypertension (systolic blood pressure > 240 mmHg or diastolic blood pressure > 110 mmHg), severe angina, and severe hypotensive response (decrease > 20 mmHg in systolic blood pressure from baseline). Ischemic electrocardiogram abnormalities during the test were defined as the development of ST-segment deviation of ≥ 1 mm 80 ms after the J point. A hypertensive response to exercise was defined as a maximum systolic/diastolic blood pressure ≥ 210/105 mm Hg in men and ≥ 190/105 mm Hg in women.¹⁰

Exercise Echocardiography and Imaging Analysis

Two-dimensional echocardiography was performed in 3 apical views (4-chamber, 2-chamber, and 3-chamber) and 2 parasternal views (long- and short-axis) at rest, peak exercise, and in the immediate postexercise period. Peak and postexercise images were obtained using a continuous imaging capture system, the former with the patient still exercising, the second with the patient lying on the table. Peak imaging was performed when signs

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