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Patterns of left ventricular geometry and the transition to congestive heart failure with preserved versus depressed ejection fraction
(Patrones de geometría ventricular izquierda y la transición a la insuficiencia cardíaca congestiva con fracción de eyección conservada versus deprimida)

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Abstract (english)

Analysis of cross-sectional and follow up clinical studies, of hypertensive patients with the different left ventricular geometric patterns, provide plausible explanations for the transition from hypertensive heart disease to the two distinct phenotypes of systolic and diastolic congestive heart failure. According to the LIFE study treated-uncomplicated patients, with normal ventricular geometry (12%), concentric remodeling (11 %) and concentric hypertrophy (34 %), may evolve to the eccentric hypertrophy pattern. Patients with the eccentric hypertrophy pattern have selective sympathetic activation and progressive enlargement of the left ventricular cavity with thinning of its walls. This pattern goes on to a stage of systolic dysfunction with diminished ejection fraction and enhanced degradation of the collagen matrix. On the other hand, patients with the concentric hypertrophy pattern have predominant activation of the renin-angiotensin-aldosterone system and progressive shrinking of the left ventricular cavity with thickening of its walls. This pattern usually precedes the stage of diastolic heart failure with preserved ejection fraction, impairment of relaxation and increased deposition of collagen in the myocardial interstitium. Thus, ventricular remodeling preceding diastolic heart failure is opposite to that of hypertensive patients who go on to develop systolic heart failure.

Keywords (english): Left ventricular geometry, Congestive heart failure. Systolic heart failure, Diastolic heart failure, Essential hypertension

Resumen (español)

El análisis de los estudios transversales y longitudinales, de pacientes hipertensos con diferentes patrones de geometría ventricular izquierda, permite postular posibles mecanismos fisiopatológicos para explicar la transición de la cardiopatía hipertensiva hacia los dos fenotipos conocidos de insuficiencia cardiaca. De acuerdo con el estudio LIFE, los pacientes hipertensos no complicados, con patrones de geometría ventricular normal (12 %), remodelado concéntrico (11 %) e hipertrofia concéntrica (34 %), pueden evolucionar hacia la hipertrofia excéntrica. Pacientes con este último patrón geométrico se caracterizan por tener activación simpática y aumento progresivo aumento del tamaño de la cavidad ventricular con disminución del espesor relativo de sus paredes. El deterioro de la función ventricular y la degradación del colágeno intersticial predisponen a la insuficiencia cardiaca con función sistólica deprimida. Por el contrario, los pacientes con

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hipertrofia ventricular concéntrica tienen activación del sistema renina-angiotensina-aldosterona y aumento progresivo del grosor de las paredes ventriculares, sin cambios en el tamaño de la cavidad. La aparición, de los síntomas de insuficiencia cardiaca, se acompaña de alteraciones de la distensibilidad ventricular, aumento en la síntesis del colágeno intersticial y función ventricular sistólica normal. En otras palabras, las alteraciones progresivas de la geometría y de la función ventricular izquierda, que preceden a la aparición de los síntomas y signos de insuficiencia cardiaca, permiten explicar la transición de la cardiopatía hipertensiva hacia la insuficiencia cardiaca con función ventricular normal o anormal.

Palabras clave (español)*:* Geometría ventricular izquierda, Insuficiencia cardiaca congestiva, Insuficiencia cardíaca sistólica, Insuficiencia cardíaca diastólica, Hipertensión arterial esencial

Introduction

Essential hypertension and its immediate consequence, hypertensive heart disease, are the most common underlying causes of congestive heart failure. Clinical studies had initially demonstrated the presence of two distinct phenotypes of cardiac morphological and functional abnormalities, in the population of hypertensive patients with congestive heart failure: **1.** Left ventricular concentric hypertrophy, **with preserved ejection fraction** and abnormal diastolic function and **2.** Left ventricular eccentric hypertrophy with **depressed ejection fraction** (1). These two phenotypes are known as diastolic heart failure and systolic heart failure respectively (2-6). More recently, prospective investigations have shown a marked heterogeneity of ventricular geometry in patients with diastolic heart failure. Although, concentric remodeling and concentric hypertrophy predominate, eccentric hypertrophy with preserved ejection fraction can also be present in twelve to sixteen percent of these patients (7,8).

Transition from compensated ventricular hypertrophy to congestive heart failure

Why compensated left ventricular hypertrophy evolves to congestive heart failure is not completely understood. Concentric hypertrophy used to be considered the predominant cardiac adaptation to hypertension and myocardial infarction the responsible mechanism for the transition to systolic heart failure. However, patients with concentric hypertrophy may develop a low ejection fraction, without interval myocardial infarction. Thus, a low ejection in fraction may develop in 20% of subjects without interval myocardial infarction and in 44% of subjects with interval myocardial infarction, during long-term follow-up. Of the subjects who developed a reduced ejection fraction, the relative wall thickness at follow-up was consistent with a concentric, rather than eccentric, phenotype. It should be emphasize that, a change from concentric to eccentric hypertrophy, does not occur in these patients. (9). Rame JE et al had previously reported that, of 159 predominantly hypertensive African-American patients with LV hypertrophy and a normal ejection fraction, 28 (18%) developed a reduced ejection fraction, after a median follow-up of approximately 4 years. Only 5 of these patients (22 %) had an interval myocardial infarction (10). Moreover, sequential admissions, of patients with heart failure and preserved ejection fraction documented a significant decline in LV systolic function at follow-up. None of these had presented to the hospital for any cause other than routine outpatient department (11). Similarly, it is not known why patients with concentric hypertrophy develop congestive heart failure, with preserved left ventricular ejection fraction (12). Nonetheless, the transition from hypertensive heart disease, to the two described phenotypes of congestive heart failure, may be partially explained by the geometric patterns of cardiac adaptation to high blood pressure (13-18) and their respective neurohormonal (19-24), hemodynamic (25-28) and extracellular matrix profiles (29).

Patterns of left ventricular hypertrophy and their respective neurohormonal and hemodynamic profiles in hypertensive patients

The morphologic cardiac adaptation to high blood pressure was initially described by de Simone et al (15) and Ganau et al., (16) in the late 1980´s and early 1990´s respectively. Contrary to conventional knowledge, these investigators found in untreated hypertensive patients that concentric hypertrophy is neither the only one pattern of ventricular adaptation nor the most frequent one. Four patterns of left ventricular anatomy were characterized by means of two-dimensional echocardiography. Ratio of wall

thickness to chamber dimension and gender-specific ventricular mass index were used to determine ventricular geometry. Fifty two per cent of the patients had normal geometry and 13 % concentric remodeling. Concentric hypertrophy was present in only 8 % compared to 27 % of patients with eccentric hypertrophy.

Left ventricular hypertrophy usually occurs by an increase in chamber size or wall thickness. The two-tiered classification proposed by Ganau et al (16) was based on the relative thickness of the left ventricular wall in proportion to the diameter of the ventricular chamber. Since, this classification does not consider possible isolated and independent changes in ventricular dilatation or in wall thickness, Khouri MG et al recently proposed a four-tiered classification (17). Left ventricular mass and volume were estimated by means of cardiac magnetic resonance imaging, in a multiethnic population of Dallas County. Wall thickness or concentricity was determined from the ratio of ventricular mass to ventricular volume and the left ventricular diastolic volume was index to body surface area. Eccentric hypertrophy was subclassified into dilated hypertrophy and indeterminate hypertrophy. Concentric hypertrophy was also subclassified into thick hypertrophy and thick-dilated hypertrophy. According to this new classification, ventricular adaptation may result from an independent increase in wall thickness and/or chamber dimension rather than the effect of their interaction. The subclassification of eccentric hypertrophy into dilated hypertrophy and indeterminate could, according to the authors, provide a plausible explanation for the apparently higher prevalence of eccentric versus concentric hypertrophy in hypertensive patients. Furthermore, the new phenotypes of thick and thick-dilated hypertrophy could represent a transition from concentric hypertrophy to eccentric hypertrophy and possibly to systolic heart failure without an interval myocardial infarction (7-11,18).

The neurohormonal and hemodynamic profiles of hypertensive patients with the different ventricular geometric patterns have also been studied (19-28). Thus, catecholamine serum levels were found to be highest in patients with eccentric hypertrophy followed by concentric hypertrophy, concentric remodeling and normal geometry. Concordantly, the density of β-AR in lymphocytes was down regulated and the intracellular content of cAMP markedly decreased, in the presence of eccentric hypertrophy (19). Compared to normal geometry and to the other geometric patterns, the highest values of plasma renin and of natriuretic peptides corresponded to those patients with concentric hypertrophy (20-22). Conversely, other studies have found the lowest values of plasma renin activity and highest serum values of aldosterone in patients with eccentric hypertrophy (23,24). These patterns of ventricular hypertrophy are at the extremes of the hemodynamic spectrum. Concentric remodelling and concentric hypertrophy are characterized by an elliptic left ventricle, normal stroke volume and high peripheral vascular resistance. On the contrary, patients with eccentric hypertrophy have a spheric left ventricle, increased stroke volume and low peripheral vascular resistance (25-28).

Change in left ventricular geometry with antihypertensive therapy

Medical treatment of hypertensive patients is known to favorably influence left ventricular hypertrophy. However, few studies have paid attention to the effects of the different drugs, on the ventricular geometric patterns. The **LIFE** study assessed the change induced by treatment with atenolol or losartan, supplemented with thiazide-type diuretics, calcium antagonists and angiotensin converting enzyme inhibitors on left ventricular geometry at one and four years (30,31). The most common patterns, at baseline, were eccentric and concentric hypertrophy. Normal geometry and concentric remodeling were present only in 20 and 7 % respectively. At one year after treatment, the prevalence of normal geometry increased from 20 % to 51 % and concentric hypertrophy diminished from 24 to 6 %, **It should emphasized that, 34 % of the patients with concentric hypertrophy, 11 % of those with concentric remodeling and 12 % with normal geometry developed eccentric hypertrophy**. Moreover, 55 % of the patients with this geometric pattern experienced no change during follow up. **Therefore, eccentric hypertrophy was not only the most refractory pattern to treatment, but it became a common final pathway for the other geometric patterns**. At four years after treatment, in middle age and older patients, the percentage of patients with concentric hypertrophy decreases markedly, where as, the percentage of patients with eccentric hypertrophy diminishes minimally (31). The VIPE-candesartan investigation, a follow up study during 6 months, showed similar findings (32).

Prospective investigations indicate that left ventricular eccentric and concentric hypertrophy are risk factors for abnormalities of left systolic and

diastolic ventricular function respectively. Thus, The Cardiovascular Health Study analyzed left ventricular mass as a risk factor, for the development of a depressed left ventricular ejection fraction within five years (33). In this study, eccentric hypertrophy was significantly associated with the development of a depressed left ventricular ejection fraction; where as, concentric remodeling and concentric hypertrophy were not. The ARIC study (34) showed that, again eccentric hypertrophy was strongly related to left ventricular systolic dysfunction, and Verdechia et al., found a nine-fold higher risk for systolic heart failure, of hypertensive patients with asymptomatic left ventricular dysfunction (30). These results clearly indicate that, in asymptomatic hypertensive patients, eccentric hypertrophy is a precursor for depressed left ventricular ejection fraction and left ventricular dysfunction is a risk factor for systolic heart failure. Consequently, one should ask: do these three obviously related stages, of the natural history of hypertensive heart disease, have a common underlying pathogenic mechanism?

Neurohormonal similarities of the eccentric pattern of left ventricular hypertrophy, with those of asymptomatic left ventricular dysfunction

The **SOLVD** prevention trial assessed the effects of enalapril on mortality and on the risk of developing heart failure, in asymptomatic patients with left ventricular systolic dysfunction. About one third of the patients included in this study was hypertensive and had left ventricular systolic dysfunction (36). The neurohormonal profile of these patients was remarkably similar to that of asymptomatic hypertensive patients with eccentric hypertrophy (19,23,37). Sympathetic activation and "normal" or low serum renin levels were present in both groups of patients. Since, the degree of sympathetic activation, as expressed by the norepinephrine serum levels, was the strongest predictor for the development of systolic heart failure (38); one is tempted to postulate that chronic exposure of myocardial cells to catecholamines and cardiac remodeling are the responsible mechanisms for the transition, from hypertensive eccentric hypertrophy to asymptomatic left ventricular dysfunction and ultimately to systolic heart failure (figure 1). This transition is characterized by a progressive increase in left ventricular cavity size, thinning of wall thickness and diminished systolic function (39). The favorable results on survival and remodeling observed in the SOLVD (40), REVERT (41) and CARMEN trials (42), which used beta-adrenergic blockers in hypertensive patients with asymptomatic left ventricular dysfunction, would support this hypothesis.

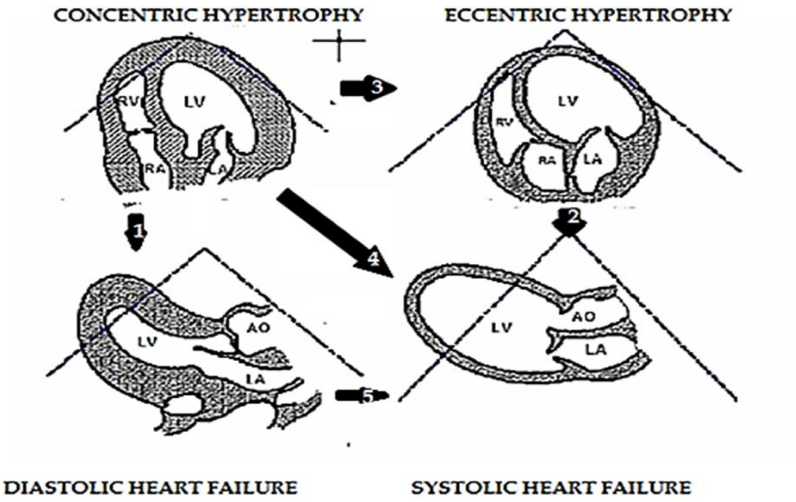

Figure 1. Patterns of left ventricular geometry and the transition to systolic and diastolic hear failure. Left ventricular concentric and eccentric hypertrophy are the precursors of diastolic **(Arrow 1)** and systolic heart failure respectively **(Arrow 2)**. Concentric hypertrophy may evolve to the eccentric pattern **(Arrow 3)** and to systolic heart failure **(Arrow 4)**, without interval myocardial infarction. Patients with diastolic heart failure may also evolve to systolic heart failure **(Arrow 5)** (Adapted from Davila-Spinetti et al. Rev Venez Endocrinol Metab 2012; 10:5-19. Ref. 90).

Neurohormonal similarities of the concentric pattern of left ventricular hypertrophy, with those of diastolic heart failure

The SOLVD registry also included heart failure patients with preserved systolic function. These patients had a predominant activation of the renin_angiotensin-aldosterone system (**RAAS**) (43). More recent studies indicate that congestive patients, with preserved ventricular systolic function, also have very high levels of natriuretic peptides (44). This neurohormonal profile is very similar to that of an asymptomatic hypertensive patient with concentric hypertrophy (20-22). These obvious similarities would suggest that activation of the **RAAS** could be one of the responsible mechanisms, for the transition from asymptomatic concentric hypertrophy to diastolic heart failure (Figure 1). However, the results of the **CHARM** (45) and **PRESERVED** studies (46), which treated diastolic heart failure with angiotensin II antagonists, showed no survival benefits. These results are not only unfavorable, but would appear to be "paradoxical", when analyzed, in the context of **the SOLVD, REVERT** and **CARMEN** trials of patients with systolic heart failure. Thus, one would expect that, by antagonizing the predominant neurohormonal system in diastolic heart failure (ie. RAAS activation), survival would be improved as in systolic heart failure (39-42). Consequently, in order to improve our perception about the complexity of the transition from hypertensive heart disease to diastolic heart failure, other abnormalities of the structure and function of the hypertensive heart should be now be considered (47-52).

Myocardial structure, form and function in the transition to systolic and diastolic heart failure

Myocardial structure, form and function differ in hypertensive patients with systolic or diastolic heart failure. Biopsy samples, analized with histomorphometry and electron microscopy, have demonstrated that myofibrillar density is lower in the former, where as, cardiomyocyte diameter is higher in the latter. Cardiomyocyte passive force correlates with myocardial stiffness and left ventricular end-diastolic pressure (5). When compared to control subjects and to hypertensive patients, diastolic heart failure patients have variable degrees of left ventricular hypertrophy, smaller ventricular volumes, impaired ventricular relaxation and preserved ejection fraction (44,53,54). This pattern of cardiac remodeling was recently confirmed by Gonzalez A. et al (55). Ventricular filling pressures were measured in heart failure patients with preserved ejection fraction. Filling pressures were higher than 15 mm Hg in the presence of smaller ventricular volumes, higher ejection fractions and larger relative wall thickness. Thus, the ventricular remodeling process, of the hearts of those hypertensive patients who go on to develop diastolic heart failure, seems to be characterized by progressive shrinkage of the ventricular volumes, thicker ventricular walls and impairment of ventricular relaxation. Although these studies are cross-sectional, follow up clinical investigations indicate that factors usually associated with diastolic heart failure, like advancing age, female sex, smoking and diabetes mellitus, are positively associated to this particular pattern of cardiac remodeling (56-58). Moreover, it should be emphasized that, as already described, transition to systolic heart failure follows an opposite pattern of cardiac remodeling (39-42). As a result, the left ventricle of diastolic heart failure patients is smaller, the relative wall thickness is also larger and systolic function is preserved (table 1) (53). These cardiac abnormalities are mostly secondary to changes in the biology of myocytes (59,60). However, the process of cardiac remodeling is not limited to myocardial cells. Recent clinical and experimental investigations indicate that the extracellular matrix is actively involved in these processes (29,61-65).

The extracellular matrix in hypertensive heart disease

The cardiac adaptative responses to hypertension take place in the cellular as well as in the extracellular compartment of the myocardium. The extracellular matrix used to be considered as a static tissue, which provided structure and support for myocyte alignment. However, it is currently seen as a complex system of dynamic interactions that determine collagen content and influence cardiac remodeling (29,61,62). Extracellular matrix structure and integrity mostly depends on collagen synthesis and the equilibrium between extracellular enzymes that favor matrix degradation and enzymes that favor inhibition of matrix degradation. The former are collectively known as metalloproteinases (MMPs) and the latter as tissue inhibitors of metalloproteinases (TIMPPs). Both kinds of enzymes are differentially regulated by cytokines, neurohormones and oxidative stress (63-67).

Collagen content (ie. Myocardial fibrosis) and the activity of the MMPs and TIMPs vary in the two types of cardiac remodeling leading to diastolic and systolic cardiac failure (68). Myocardial fibrosis, in hypertensive patients with predominant left ventricular concentric hypertrophy and diastolic heart failure, parallels the increase in heart weight (69). Cross-sectional and follow up studies have shown that the activity of MMPs and TIMPs which enhance collagen deposition is increased (53-55,70). On the contrary, disruption of the extracellular matrix, loss of collagen cross-linking and diminished of connectivity of collagen network with individual myocytes, characterize the hearts of patients and experimental models with systolic heart failure (71-75). The equilibrium is now shifted to MMPs which increase collagen degradation (table 1) (54,76). Thus, excessive collagen degradation promotes left ventricular dilatation and systolic dysfunction, where as excessive collagen deposition increases left ventricular fibrosis and impairs diastolic function (77).

Table 1. Cardiac remodeling in the transition from hypertensive heart disease to systolic and diastolic heart failure

Cardiac remodeling	Systolic heart failure	Diastolic heart failure
Cardiac mass	Increases	Increases
Relative wall thickness	Decreases	Increases
Left ventricular volumes	Increase	Decrease
Ventricular relaxation	Mildly impaired	Grossly impaired
MMPs activity	Increases	Decreases
TIMPs activity	Decreases	Increases
Collagen deposition	Decreases	Increases
Collagen cross-linking	Decreases	Increases

MMPs: Matrix metalloproteinases. **TIMPs**: Tissue inhibitors of matrix metalloproteinases (Adapted from Davila-Spinetti et al. Rev Venez Endocrinol Metab 2012; 10:5-19. Ref. 90)

Therapeutic implications of left ventricular geometry in the transition from ventricular hypertrophy to systolic and diastolic heart failure

Drugs available for the pharmacologic treatment of essential hypertension include: Diuretics, Calcium channel blockers, Angiotensin II receptors antagonists, Angiotensin converting-enzyme inhibitors and Beta-adrenergic blockers. Pharmacologic treatment of essential hypertension reverses cardiac remodeling and reduces the risk of cardiovascular events. However, the effectiveness of these drugs in the prevention of heart failure has been the subject of intense controversy and clinical research. A recent meta-analyisis, which included randomized controlled trials published from 1997 through 2009 with a total of 223.313 patients, concluded that calcium channel blockers were the least effective first- line antihypertensive agents, for the prevention of heart failure. Conversely, diuretics, angiotensin II receptors antagonists and angiotensin converting-enzyme inhibitors were found to be the most effective drugs for the treatment of hypertensive patients, at high risk of developing heart failure. Other meta-analysis has focused on hypertension treated with calcium channel blockers and incident heart failure. Studies were eligible if they were randomized clinical trials, performed comparisons of calcium channel blockers versus active control and provided data regarding incident HF. A total of 156,766 patients were randomized to calcium channel blockers or control, with a total of 5,049 events. The analysis indicated a significant increase in the diagnosis of HF in patients allocated to calcium channel blockers. This effect observed was independent of incident myocardial infarction (78-82).

Calcium channel blockers increase the activity of the sympathetic nervous system, in patients with essential hypertension. Amlodipine, despite being an agent with an intrinsically long pharmacokinetic elimination half-life, causes a small but significant increase activation of the sympathetic nervous system as assessed by multiple markers (ie., Serum norepinephrine, Heart rate variability and Muscle nerve sympathetic activity) (83-85).

Sustained activation of the sympathetic nervous system has adverse effects on myocardial cells. It promotes apoptosis, necrosis and eccentric remodeling (86). Experimental studies have shown that chronic beta-adrenergic activation promotes changes in left ventricular geometry, through chamber dilatation and not via modifications of myocardial systolic function, in hypertensive rats with left concentric hypertrophy (75, 77,87-90). So, a plausible explanation, for the association of calcium channel blockers with systolic heart failure in hypertensive patients, would be an enhancement of sympathetic activation and its deleterious effects on left ventricular geometry. Thus, a report from our institution indicates that, in hypertensive patients with eccentric left ventricular hypertrophy, calcium channel blockers

favor progressive cardiac remodeling, whereas beta-adrenergic blockers may reverse remodeling (91). Consequently, one should ask: hypertensive patients receiving calcium channels should have periodical assessment of left ventricular geometry by two-dimensional echocardiography? (92-95). Finally, recent reports on long-term follow-up studies confirmed that the risk of heart failure varied with the left ventricular hypertrophy pattern. Eccentric and concentric hypertrophy predisposed to heart failure with reduced and preserved ejection fraction respectively (96-100).

In summary, analysis of cross-sectional and follow up clinical studies, of hypertensive patients with different geometric patterns of cardiac adaptation to hypertension and their respective echocardiographic, neurohormonal, collagen metabolism and genetic profiles, provide plausible explanations for the transition from hypertension and hypertensive heart disease to the two distinct phenotypes of systolic and diastolic congestive heart failure. Since, the increased risk of systolic heart failure, described with the use of calcium channel blockers in hypertensive heart failure, could be related to the underlying left ventricular geometry pattern; a fundamental question should be asked: What is the current role of left ventricular geometry, as determined by two-dimensional echocardiography, in the initial evaluation, treatment and monitoring of patients with hypertensive heart disease?.

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