Left Ventricular Remodeling Patterns in Chronic Heart Failure

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ABSTRACT:

BACKGROUND:
Patients with heart failure show a wide spectrum of changes in left ventricular volume, mass, and function.

OBJECTIVE:
The aims of this study were to define the patterns of left ventricular structural and functional remodeling and consider their clinical implications in patients with chronic heart failure.

PATIENTS AND METHODS:
Two-dimensional echocardiograms were obtained for patients with chronic heart failure in Baghdad teaching hospital during the period from February 2009 to February 2011 and were used to calculate left ventricular volume, mass, geometry, and ejection fraction. Inclusion required the diagnosis of heart failure in symptomatic patients on medical therapy. Measures of left ventricular size or function were not used as inclusion or exclusion criteria.

RESULTS:
Two hundred and eighty (280) patients were included in this study of whom 154 were males and 126 were females. The mean age of patients was 58 ± 17 years. Plots of ejection fraction against left ventricular end-diastolic volume showing an inverse curvilinear relation allowed a description of 4 remodeling patterns. Pattern A (n = 58) was defined as normal end-diastolic volume (<91 ml/m2) and normal ejection fraction (>50%); 67.24% of these patients showed left ventricular hypertrophy or concentric remodeling. Pattern B (n = 58) was defined as normal end-diastolic volume and depressed ejection fraction; hypertrophy or concentric remodeling was present in 65.51%. Pattern C (n = 153) was defined as increased end-diastolic volume and depressed ejection fraction; eccentric hypertrophy was present in 94.77%. Pattern D (n = 11) was defined as increased end-diastolic volume and normal ejection fraction; eccentric hypertrophy was present in 81.81%.

CONCLUSION:
These patterns of remodeling encompass a wide spectrum of geometric changes with different clinical and pathophysiologic features and possibly different management strategies.

KEY WORDS: left ventricle, remodeling, heart failure

INTRODUCTION:
Chronic heart failure is a progressive process with a change in the geometry and structure of the left ventricle such that the chamber dilates, hypertrophies, and becomes more spherical. This process is referred to as cardiac remodeling. (1) This is true in patients with systolic heart failure when the end result is a large left ventricular (LV) cavity with abnormal geometry, afterload excess, and low ejection fraction (EF). However, some patients show substantial systolic dysfunction while maintaining normal or near-normal LV end-diastolic volume (EDV). (2,3) Still others with normal LV chamber size and systolic function and diastolic dysfunction also have considerable disability and a poor prognosis from diastolic heart failure. (4,5) These disparate patterns of LV remodeling are widely recognized, but there is a continuing controversy about the relative importance of structural versus functional abnormalities in the failing heart. Some focus on LV volume rather than EF (6) whereas others highlight EF as a powerful predictor of clinical outcome. (7) Such debates point to the broad spectrum of alterations in LV volume, mass, and function in patients with chronic heart failure (8,9) but the potential importance of a more comprehensive description of LV remodeling is not emphasized. Accordingly, the present study hypothesized that a combination of structural and functional parameters might provide a more rational, comprehensive, and useful description of LV remodeling. To achieve this, LV volume, mass,
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and geometry (mass/volume [M/V] and shape), as well as EF were measured in patients with chronic heart failure and 4 patterns of ventricular remodeling that have different pathophysiologic features have been described.

METHODS:
This study included 280 patients with chronic heart failure who were admitted to Baghdad teaching hospital between February 2009 and February 2011 of whom 154 were males and 126 were females. The mean age of patients was 58 ± 17 years. Chronic heart failure was considered present if the patient had a history of signs and symptoms of heart failure and was clinically stable on optimal medical therapy that included angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents. Patients with valvular and congenital heart disease were excluded. LV size and/or function were not used as inclusion or exclusion criteria. Two-dimensional echocardiograms were done using Envisor echocardiography device from Philips and 2.5-3.5 probe. Endocardial silhouettes from the end-diastolic and end-systolic frames of the apical 4- and 2-chamber views were manually digitized to obtain LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) using the method of discs. EF was calculated as (EDV - ESV) / EDV×100. LV mass was calculated at end-diastole as 5/6 × LV short-axis myocardial area × LV cavity length × density of muscle (1.055). LV shape at end-diastole was evaluated by calculating the ratio of the short-axis cavity area to the long-axis cavity area. This index approaches unity as geometry approaches that of a sphere. The left atrial area, measured from the apical 4-chamber view, was considered an index of left atrial size. The upper limit of normal for EDV is 91 ml/m². Normal LV mass is <105 g/m². The range of normal for the M/V ratio is 1.1 to 1.3. These normal values are virtually identical to those derived using cardiac magnetic resonance imaging in asymptomatic subjects who did not have evidence of cardiovascular disease. EF was plotted against EDV for all 280 patients, and individual coordinates were assigned to 1 of 4 groups (patterns) defined on the basis of normal and abnormal values for EF and EDV. Pattern A was defined as normal EDV (≤91 ml/m² body surface area) and normal EF (≥50%). Pattern B was defined as normal EDV and low EF. Pattern C was defined as increased EDV and low EF. Pattern D was described as increased EDV and normal EF. Statistical analysis Data were presented as means ± SD. Differences between groups were assessed using 1-way repeated-measures analysis of variance with all pair-wise multiple comparisons made using Tukey test. A p value < 0.05 was considered a significant difference.

RESULTS:
In the entire population of 280 patients with heart failure, EF ranged from 15% to 68% and was normal in 67 patients. EDV ranged from 35 to 256 ml/m² and was normal in 116 patients. Data are listed in Table 1 and Figure 1. Figure 1 shows the relative EDV and EF coordinates of 4 remodeling patterns. Of 116 patients with normal EDV, 58 had normal EF (group A) and 58 had reduced EF (group B). LV enlargement was present in 164 patients, and most (93.29%) of those with increased EDV had reduced EF (group C). These data indicate that increased EDV generally predicts reduced EF, but normal EDV does not predict normal EF. Also, normal EF generally predicts normal LV EDV, but low EF does not predict LV enlargement. Average values for LV mass were similar in patients with patterns A and B. LV hypertrophy (mass >105 g/m²) or concentric remodeling (normal mass with M/V >1.3) was present in 67.24% of patients in group A, and hypertrophy alone was present in 46.55%. Findings were similar in group B. In this group, hypertrophy and/or concentric remodeling were present in 65.51%, and hypertrophy alone was present in 56.89%. LV hypertrophy was present in 94.77% of patients in group C. This combination of increased LV mass with chamber dilatation indicates eccentric hypertrophy. Despite a significantly higher LV mass, M/V was significantly lower than that seen in groups A and B. M/V was low or normal in 78.43% of group C patients. Less than 5% of patients in group C showed eccentric remodeling (chamber enlargement with normal LV mass). Nine of 11 patients in group D had LV hypertrophy and normal or low M/V. Thus, 81.81% of this small group had eccentric hypertrophy. Left atrial enlargement was present in all 4 groups. The group with LV enlargement and low EF (group C) had a larger left atrial area than that in groups A, B, and D, but this trend did not achieve statistical significance.
**Table 1:** Left ventricular (LV) structure and function in 280 patients with chronic heart failure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pattern</th>
<th>A (n = 58)</th>
<th>B (n = 58)</th>
<th>C (n = 153)</th>
<th>D (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>A</td>
<td>57 ± 6</td>
<td>40 ± 6*</td>
<td>31 ± 8*†</td>
<td>53 ± 3†‡</td>
</tr>
<tr>
<td>EDV (ml/m²)</td>
<td>A</td>
<td>68 ± 10</td>
<td>80 ± 9</td>
<td>138 ± 36†↑</td>
<td>105 ± 12†↑</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>A</td>
<td>101 ± 17</td>
<td>106 ± 16</td>
<td>148 ± 32†*†</td>
<td>125 ± 22†*†</td>
</tr>
<tr>
<td>M/V</td>
<td>A</td>
<td>1.5 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>1.1 ± 0.2†*†</td>
<td>1.2 ± 0.1†*†</td>
</tr>
<tr>
<td>LV shape</td>
<td>A</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td>A</td>
<td>24 ± 8</td>
<td>23 ± 8</td>
<td>28 ± 8</td>
<td>23 ± 6</td>
</tr>
</tbody>
</table>

* p < 0.05 versus pattern A.
† p < 0.05 versus pattern B.
‡ p < 0.05 versus pattern C.

**Figure 1:** The curvilinear relation of LV EF to EDV in 317 patients with chronic heart failure. The lower limit of normal EF (50%) and upper limit of EDV (91 ml/m²) are shown. Patients with normal EDV showed a wide range of EF. Patients with low EF showed a wide range of EDV.

**DISCUSSION:**

The relative importance of structural and functional abnormalities in the failing heart has been debated for over 100 years. The results of this study support the hypothesis that LV remodeling is best described by a combination of structural and functional parameters. In this study, as in other previous studies, the curvilinear inverse relation between EF and EDV generally predicts that EF would be depressed when the left ventricle is dilated and preserved when EDV is normal. However, when the coordinates of EF and EDV are partitioned into groups defined using normal and abnormal values, our analysis indicates that patients with heart failure with normal EDV tend to have LV concentric remodeling or concentric hypertrophy, but normal EDV does not predict normal EF. Those with a dilated ventricle tend to have eccentric hypertrophy and low EF, but low EF does not reliably predict a large EDV. The 4 remodeling patterns described here show different pathophysiologic characteristics and it is possible that such disparate remodeling patterns would require different treatments.

Pattern A (normal EDV and normal EF): This pattern, typical of that in patients with diastolic heart failure, was seen in 20.71% of 280 patients. Most (67.24%) of these patients had concentric LV hypertrophy or concentric remodeling. This is similar to the prevalence of hypertrophic remodeling (53%) reported by Lam CSP et al. In such patients, LV systolic performance, function, and contractility is normal and diastolic function is abnormal. The signs and symptoms of systolic and diastolic heart failure are similar, but structural and functional abnormalities at the level of the whole ventricle and level of the cardiomyocyte are distinctly different. Thus, criteria for the diagnosis of diastolic heart failure require assessment of both LV structure and function. Pattern B (normal EDV and low EF): This pattern, seen in 20.71% of 280 patients, is typical of that in patients with non-dilated cardiomyopathies. In such patients, systolic functional abnormality is prominent, EF is low, and LV stroke volume is very low. Most patients in this group have LV hypertrophy or concentric remodeling. Cioffi G et
al. and Doumas A et al. showed that the clinical signs appear to be similar to those in patients with dilated cardiomyopathy, but there is some variation in clinical outcomes.(2,3) This relatively underemphasized form of systolic heart failure with a non-dilated ventricle requires more study and better definition.

Pattern C (LV enlargement and low EF): This pattern, seen in 54.64% of 280 patients, is typical of that seen in most patients with systolic heart failure. In such patients, eccentric hypertrophy is present and geometry and shape are altered, whereas LV afterload excess and a depressed contractile state contribute to a low EF. This remodeling pattern has been the target of multiple therapeutic trials and is emphasized in published guidelines for the management of heart failure.(1)

Pattern D (LV enlargement and normal EF): This pattern was present in only 11(3.92%) patients. It is usually seen in patients with regurgitant lesions of the mitral or aortic valve, but such patients were excluded from the present study. It is possible that such co-morbidities as anemia or chronic renal insufficiency contributed to the LV chamber enlargement. A relatively low prevalence of this pattern has also been found by others like Zile MR et al. (21)

LV hypertrophy is generally classified as concentric/pressure-overload or eccentric/volume-overload(8,22). In this classification, concentric hypertrophy refers to an increase in LV mass with little or no change in EDV, and LV M/V and thickness/radius ratio are increased. Linzbach AJ et al. recognized that an increase in M/V (without an increase in LV mass) identified hypertensive patients with increased risk of cardiovascular morbidity and mortality, and they applied the term concentric remodeling to this type of structural alteration.(21) As the hypertrophic process progresses and LV mass exceeds the upper limits of normal (and M/V remains high), the term concentric hypertrophy is applied. Concentric remodeling and hypertrophy were the dominant structural abnormalities in our patients with patterns A and B. The observation that systolic function was normal in patients with pattern A and depressed in patients with pattern B supported our conclusion that LV remodeling is best described by a combination of structural and functional parameters. Patients with increased EDV that is out of proportion to the increased LV mass (group C and D) are said to have eccentric hypertrophy; the M/V is low or low normal. (8) If EDV is increased without an increase in LV mass, the term eccentric remodeling could be applied. This pattern of remodeling with a low M/V is seen in patients with acute or subacute mitral regurgitation, in whom it is considered a short-term functional adaptation that provides for larger stroke volume through the Frank-Starling mechanism. If hypertrophy develops, M/V increases and may approach normal (e.g., eccentric hypertrophy in patients with chronic compensated mitral regurgitation). Linzbach AJ et al. reported that in patients with LV dilatation and inadequate hypertrophic response (e.g., myocarditis), M/V remains low and chronic eccentric remodeling or “irreversible plastic dilatation” persists (8) EF as a measure of LV systolic function is dimensionless, appropriately normalized, and does not require correction for body size. In this study of patients with chronic heart failure, EF was normal in 67 patients. Patients with heart failure with normal EF, normal chamber size, and a high prevalence of LV hypertrophy (i.e., those in group A) virtually always show abnormalities in diastolic function and said to have diastolic heart failure (24). Structural changes seen in group B are similar, but EF is depressed. In group C, structural remodeling was dramatically different, with substantial chamber enlargement, eccentric hypertrophy, and severe depression of EF. Group D had similar structural remodeling, but EF was not depressed. Certainly, a comprehensive definition of LV remodeling requires more than a single measure of structure or function. Any study of LV size and function requires a definition of the normal range of the parameters under consideration. Thus, the relative size of each group in this present study will be influenced by the definitions of normal LV volume and EF. For example, if the EF limit were set at 40% or 45% rather than 50%, the number of patients in group A would obviously increase and the number of patients in group B would decrease. Our use of a 50% limit was based on what has traditionally been considered the lower limit of normal (25) and in studies of pathophysiologic characteristics, demographics, and outcomes of patients with heart failure (4,5,14,20,26). A second limitation is that measurement of LV size and function at a single point in time may misclassify a patient with LV remodeling that is in a state of evolution. For example, patients with pattern B may have evolved from pattern A, having developed a decrease in EF with little or no increase in chamber size. Rame JE et al. and
Drazner MH et al. showed that this is relatively uncommon when concentric hypertrophy is present (26,27). It is also possible that some of those with pattern C may have evolved from pattern B. As Lopez B et al. mentioned, this could occur in patients with hypertensive heart disease and a high ratio of matrix metalloproteinase to its tissue inhibitor, 28 but progressive chamber enlargement \ appears to be uncommon in patients with concentric hypertrophy unless an interval myocardial infarction occurred (26,27). Handoko ML et al. showed that in the absence of coronary artery disease, patients with diastolic heart failure and prevalent hypertension or diabetes mellitus show progressive stiffening of the ventricle and increasing LV end-diastolic pressure without a significant change in EDV or EF(29). Thus, once hypertrophy and/or increased chamber stiffness is established, it appears that progressive chamber dilatation (to the extent seen in group C) is unlikely to occur. These issues require additional research with serial long-term studies to define the natural history of these patterns of remodeling.

CONCLUSION:
The above patterns of LV remodeling encompass a wide spectrum of geometric changes with different clinical and pathophysiologic features and possibly different management strategies.

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