Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 9, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.12.012

EDITORIAL COMMENT

Left Ventricular End-Diastolic Volume Is Normal in Patients With Heart Failure and a Normal Ejection Fraction

A Renewed Consensus in Diastolic Heart Failure*

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The study published in this issue of the *Journal* by Maurer et al. (1) provides data which, interpreted in the context of a number of recently published studies (2–8), allow us to conclude that: 1) left ventricular (LV) end-diastolic volume (EDV) is normal in the vast majority of patients with heart failure (HF) and a normal ejection fraction (HFNEF) (i.e., diastolic heart failure [DHF]); 2) the pathophysiology underlying the vast majority of patients with HFNEF (DHF) primarily reflects the development of progressive diastolic dysfunction.

See page 972

These data allow us to come full circle from consensus to controversy back to consensus in our understanding of patients with DHF.

The consensus. In 2004, a group of HF investigators and clinical scientists met in Woodstock, Vermont, and developed a consensus document that stated: ". . . it was agreed that patients with LV failure present in 1 of 2 broad categories. One type exhibits a low ejection fraction with increased end diastolic volume and preserved or reduced stroke volume. This presentation (has) traditionally (been) called systolic heart failure. . . The second group has normal or near-normal LV diastolic volume and preserved ejection fraction. This presentation (has) traditionally (been) called diastolic heart failure" (9). This consensus document did not recommend any change in current HF nomenclature: systolic HF and DHF.

The controversy. The consensus view that patients with HFNEF (or DHF) have a normal or near-normal EDV became a point of controversy in 2005. Among otherwise consistent data from multiple investigators and studies, some divergent data were reported (Table 1) (1,10,11). In 1 analysis, control subjects were compared with patients with hypertension and no HF, and patients with hypertension and HFNEF (10). In this analysis, it was reported that patients with hypertension and HFNEF had a 40% larger LV EDV compared with normal controls. This difference in EDV appeared to be driven by differences in the LV end-diastolic long-axis dimension (EDL), which was greater by an average of 16 mm; the short-axis end-diastolic dimension (EDD) was 1 mm smaller than normal controls.

In a subsequent analysis, patients with HFNEF were divided into those with and those without a history of hypertension (11). In this analysis, patients with HFNEF without hypertension had similar EDV compared with normal control subjects. This normal LV EDV resulted from a smaller EDD and a larger EDL than normal control subjects. By contrast, patients with HFNEF and hypertension had larger EDV, by an average of 24%, compared with normal control subjects. Again, the larger EDV was driven by differences in EDL, which was 6 mm larger, while EDD actually was 1 mm smaller than normal control subjects.

Consensus redefined. In the study published in this issue of the *Journal*, the Cardiovascular Health Study Data Base was used to compare selected control subjects to patients with hypertension and no HF and patients with hypertension and HFNEF. In patients with hypertension and HFNEF, the mean value of LV EDV (calculated from an M-mode echocardiographic measurement of LV minor-axis EDD) was larger by 14%, and the mean value of LV EDD was larger by 3 mm compared with normal controls. Left ventricular EDL was not measured in this study. While examination of group averages raises the question of a somewhat larger EDV in patients with HFNEF, examination of the frequency distribution of the data clearly establish that the majority, in fact 90%, of patients with hypertension and HFNEF had EDV values that fell within the normal range.

A standard method of establishing a "normal range" in any data set is to use the mean ± 2 SDs from the mean. Based on this definition, the normal range for LV EDD in this study was 4.0 to 6.0 cm. From their analysis, the authors concluded that the difference in EDV ". . . does not preclude a significant proportion of the values for left ventricular diastolic diameter in the HFNEF population remaining within the normal or reduced range even when adjusted for age, gender, body size and race. Increased

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Table 1 Three Sets of Data Analysis From Previous Publications

Subject Group	EDV	EDD	EDL	% ↑ in EDV
Vest et al. (10)				
Controls	88 ± 24	4.6 ± 0.7	10.3 ± 1.4	
Hypertension no HF	117 ± 29	5.1 ± 0.4	10.3 ± 1.4	
Hypertension HFNEF	124 ± 33	4.5 ± 0.7	11.8 ± 1.9	40
Maurer et al. (11)				
Controls	95 ± 21	4.7 ± 0.5	10.6 ± 1.1	
No hypertension HFNEF	98 ± 25	4.0 ± 0.8	11.4 ± 1.1	
Hypertension HFNEF	118 ± 29	4.6 ± 0.5	11.2 ± 1.2	24
Maurer et al. (1)				
Controls	109 ± 27	4.8 ± 0.6		
Hypertension no HF	110 ± 28	4.9 ± 0.6		
Hypertension HFNEF	124 ± 38	5.1 ± 0.8		14

Each set of data was taken from the reference listed.

EDD = left ventricular end-diastolic short-axis dimension; EDL = left ventricular end-diastolic long-axis dimension; EDV = left ventricular end-diastolic volume; HF = heart failure; HFNEF = heart failure with a normal ejection fraction; % ↑ in EDV = percent increase in LV EDV in the hypertension HFNEF group compared with the normal control group.

ventricular diameter in the heart failure normal ejection fraction group of subjects might also be explained by the presence of a few subjects with large ventricles not representative of the remainder of the heart failure normal ejection fraction group." In actuality, the data show that *only* 10% of the patients with hypertension and HFNEF had an LV EDD that exceeded the normal range. Although this can be discerned in Figure 1 of their report, to make this point more clearly, we modified this figure to indicate the normal range and identify those patients with HFNEF who fall outside the normal range (Figs. 1 and 2). It seems very likely that if a similar frequency distribution analysis had been performed in previous studies, similar results would have been obtained. Therefore, these data and this interpretation allow us to return to a consensus emphasizing that the great majority of patients with HFNEF have a normal LV EDV. These conclusions can be applied to the general population of patients with HFNEF or DHF because most patients with this diagnosis have hypertension.

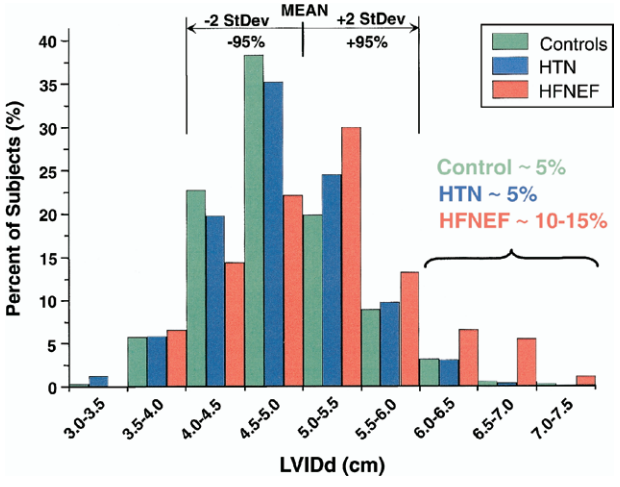

Figure 1 Histogram of Distribution of LVIDd

Normal control subjects are compared with subjects with hypertension and no heart failure (HTN) and subjects with hypertension heart failure and a normal ejection fraction (HFNEF). The normal range for left ventricular internal end-diastolic short-axis diameter (LVIDd) is marked above the graph as mean ± 2 standard deviations (StDevs) for the control group (this encompasses the 95% confidence intervals).

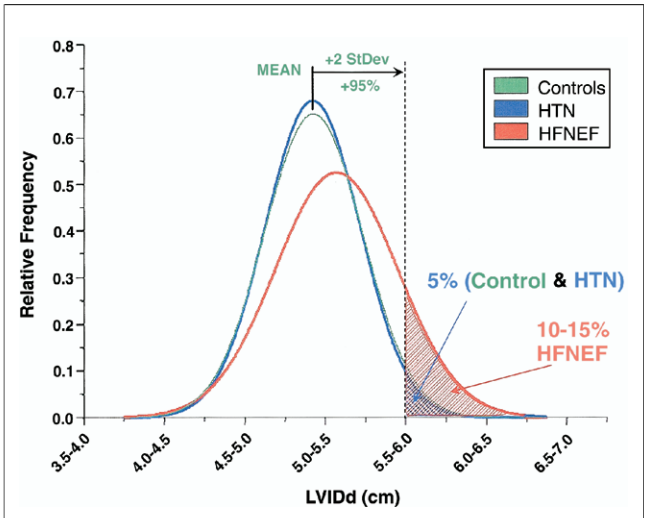

Figure 2 Gaussian Distribution of LVIDd

Frequency distribution of LVIDd demonstrating that 5% of the control subjects had an LVIDd larger than the upper limits of normal and 15% of the HFNEF subjects had an LVIDd larger than the upper limits of normal. Therefore, only 10% of the HFNEF subjects had an LVIDd larger than expected for the control group. Abbreviations as in Figure 1.

Authors versus editorialist conclusions. It should be made clear that the authors of the current study propose a somewhat different interpretation of their data than the authors of this editorial. The authors of the current *Journal* study propose the following conclusions: "As a group, HFNEF subjects have increased LV diastolic diameter. . . These data suggest extracardiac factors, via volume overload, may contribute to the pathophysiology of HFNEF. . ." However, there is an important difference between the conclusion that the mean LV EDV in patients with HFNEF or DHF is increased by 10% to 15% and the conclusion that only 10% to 15% of patients have an increased LV EDD. Exceptions to the rule are the norm in clinical medicine. Thus, it is hardly surprising that this group of patients, with significant comorbidities such as diabetes mellitus, renal insufficiency, coronary heart disease, and anemia, includes a small proportion with an increased EDD. Moreover, the finding that a few patients have an EDD greater than normal does not provide insight into the pathophysiology underlying the development of HF in the vast majority of patients with HFNEF or DHF. In contrast, the finding that >90% of these patients had an LV EDD within the normal range provides pathophysiological information crucial to the development of diagnostic, prognostic, and therapeutic tools in patients with DHF.

Importance of this redefined consensus. Why is a consensus regarding LV EDD and EDV important in patients with DHF?

1. Pathophysiology: previous studies have clearly demonstrated that a dominant pathophysiological mechanism in patients with DHF is abnormal diastolic function: specifically, slowed relaxation, increased diastolic chamber stiffness (increased slope of the diastolic pressure-volume relationship), and/or decreased diastolic distensibility (increased diastolic pressure, with no change in diastolic volume, with or without a change in the slope of the diastolic pressure-volume relationship) (2–8,12–15). As shown in Figure 3, when LV end-diastolic pressure increases with little or no change in volume, this indicates a decrease in LV diastolic chamber distensibility (point A vs. C). However, if both diastolic pressure and volume increase in a coordinate fashion along a normal diastolic pressure-volume relationship, this indicates that LV chamber distensibility has not changed (point A vs. B). The diastolic pressure-volume relationship has been measured directly in only 1 study in patients with definite DHF (3). This study showed that patients with DHF have decreased LV diastolic distensibility and increased LV diastolic stiffness. The validity of these data has not been challenged. However, some investigators have proposed an alternate hypothesis: not all patients with HFNEF have decreased distensibility, particularly those with increased LV EDV. To date, no data have been presented to support this hypothesis, and no direct measurements of diastolic function or diastolic pressure were made in the current study. Consequently, this study cannot be used to evaluate this alternate hypothesis. Even in the presence of an increased LV EDV, the LV pressure-volume curve can be displaced upward indicating decreased distensibility (point A vs. D). Thus, an increased LV EDV does not exclude decreased distensibility. Therefore, both previous and current studies support the consensus that there are dominant abnormalities in diastolic function in the majority, if not all patients, with DHF or HFNEF.
2. Treatment: to date, no randomized clinical trial has defined a clearly effective management strategy to reduce mortality and morbidity in patients with DHF. Developing effective management will depend on defining the correct target(s) for therapy. In systolic HF, increased EDV (and eccentric remodeling) has been shown to be an important therapeutic target (1). Current and previous data make it clear that EDV should not be the target for DHF (1). Rather, having consensus on EDV allows us to select LV concentric remodeling, LV hypertrophy, and diastolic dysfunction as more fruitful targets.
3. Comorbidities: one likely explanation for the 10% to 15% of patients with HFNEF who have an increased EDV is the presence of significant co-morbid conditions that commonly increase intravascular volume. In the current study, patients with HFNEF had a high prevalence of anemia (19%), severe chronic renal failure (8%), obesity (29%), coronary artery disease (58%), and diabetes mellitus (30%) compared with the other 2 groups. The effects of these co-morbid factors were not selectively examined in the 10% of HFNEF patients with an increased EDV, but they are likely to be co-dependent.

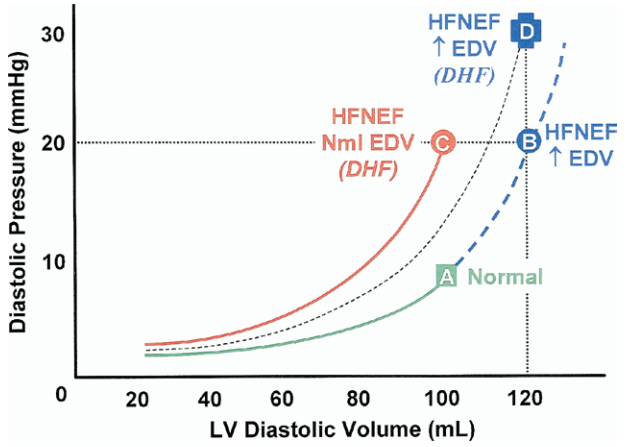

Figure 3 **Schematic Representations of Possible Diastolic Pressure-Volume Relationships in Heart Failure**

The normal end-diastolic pressure-volume point is marked as point A. When diastolic pressure increases with little or no change in volume, this indicates a decrease in left ventricular (LV) chamber diastolic distensibility (point A vs. C). However, if both diastolic pressure and volume increase in a coordinate fashion along a normal diastolic pressure-volume relationship, this indicates that LV chamber distensibility has not changed (point A vs. B). However, even in the presence of an increased LV end-diastolic volume (EDV), the LV pressure-volume curve can be displaced upward indicating decreased distensibility (point A vs. D). Thus, an increased LV EDV does not exclude decreased distensibility. Data from the current and previous studies suggest that the vast majority of patients with heart failure and a normal ejection fraction (HFNEF) or diastolic heart failure (DHF) have a diastolic pressure-volume relationship represented by the curve that intersects point C.

Study limitations. The percentage of patients that fall within versus outside the normal range in HFNEF is critically dependent on the inclusion and exclusion criteria used to define the population, and details of the methods, procedures, and technology used by a core echocardiography laboratory. For example, depending on the inclusion and exclusion criteria used, even data from the Cardiovascular Health Study have considerable variation (1,12,13). In 2 previous Cardiovascular Health Study publications, the mean LV EDD in patients with HFNEF was not statistically different from the mean LV EDD in the control group. In addition, when data from 3 Cardiovascular Health Study publications are compared, there is a difference between the mean values of LV EDD in the control groups reported in each study. Therefore, even using a carefully run core laboratory, differences in inclusion and exclusion criteria may create enough variability that the small differences in the mean value of LV EDD in the HFNEF patients versus

control subjects reported in the study in this issue of the *Journal* have limited clinical importance.

A patient characteristic that could account for variation in LV EDV between published studies is the extent of LV hypertrophy. In this regard, compared with other published databases, the Cardiovascular Health Study database includes patients with only mild LV hypertrophy as demonstrated by an average 1-mm increase in posterior wall thickness.

Another limitation of the current study is the use of a single M-mode short-axis dimension measurement to calculate EDV. In addition, it was possible to make this M-mode measurement of LV EDD in *ONLY* 86 of the 167 patients with HFNEF (i.e., ONLY 51%). Therefore, the study results are based on 86, not 167 patients, making this study of only modest size and/or power. It is also possible that the inability to make this measurement systematically excluded certain patient groups in whom echocardiographic windows are problematic.

Given these limitations, it is important to be cautious in interpreting these data. The authors of the current study propose that "extra-cardiac factors, via volume overload" contribute to the pathophysiology of DHF. However, previous studies have shown that patients with acutely decompensated DHF actually have a *reduced* LV EDV compared with the EDV present after treatment (14,15). The authors did not define nor did they examine any "extra-cardiac" factors. If by this term they refer to changes in arterial compliance or ventricular-vascular coupling, 3 recent studies have shown that these factors do not play a role in the development of DHF (5,7,8). Instead, available evidence suggests that the development of DHF primarily reflects progressive diastolic dysfunction (2–8).

Conclusions. The great majority of patients with HFNEF (i.e., DHF) have a normal LV EDV. The pathophysiology underlying DHF reflects the development of progressive diastolic dysfunction. When correctly interpreted, the study in this issue of the *Journal* supports these conclusions, removes any remaining controversy regarding LV EDV in patients with DHF, and redefines a consensus in CHF pathophysiology.

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