Heart failure (HF) is a major public health problem, currently affecting an estimated 14 million Europeans. Clinically overt HF has a poor prognosis. More than 40% of patients die and approximately 25% are re-admitted to the hospital within 1 year following their first hospitalization. Consequently, HF leads to high healthcare costs, currently exceeding those of cancer. Impairment of left ventricular (LV) diastolic function as well as systolic function appear very early in the course of heart disease. Recent HF guidelines, therefore, place special emphasis on the detection of subclinical LV dysfunction and the timely identification of risk factors for HF. Conventional echocardiography combined with new imaging techniques such as tissue Doppler and tissue tracking are sensitive tools to detect early subclinical deterioration of LV function. Community-based studies revealed a higher prevalence of LV systolic and diastolic dysfunction using the new echocardiographic imaging techniques. Future prospective studies will clarify the hitherto unknown prognosis associated with early symptom-free LV dysfunction.

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Keywords
diastole • echocardiography • heart failure • left ventricle • strain • systole
• tissue Doppler imaging

Systolic and diastolic left ventricular dysfunction: from risk factors to overt heart failure

prevalence estimates for HF staging and underscored the magnitude of the population at risk for progression to overt HF. Overall, 56% of adults 45 years of age or older were classified as being in stage A (risk factors) or B (asymptomatic LV dysfunction) [3]. Transition from stage B to stage C is associated with a fivefold increase in mortality risk [2], which underscores the importance of correctly identifying persons at stage B for early diagnosis and intervention.

Role of echocardiography in HF staging
A routine physical examination does not allow diagnosing systolic or diastolic LV dysfunction in the preclinical phase (stage B). Similarly, a physical examination cannot accurately characterize the LV volumes and cardiac output. As a rapid and accurate modality, echocardiography can improve the noninvasive detection and definition of the hemodynamic and morphologic changes in HF [3]. Moreover, impairment of LV diastolic function, longitudinal systolic function and midwall fractional shortening might appear very early in the course of heart disease.

The echocardiographic techniques to assess early subclinical changes in systolic and diastolic LV function have evolved rapidly over the past 10 years. Nowadays, tissue Doppler imaging (TDI) and tissue tracking provide additional information about global and regional cardiac function and, beyond classical M-mode and 2D echocardiography and pulsed-wave Doppler. TDI measures the velocity of mitral annular motion or myocardial wall, which reflects the shortening and lengthening of the myocardial fibers along the LV long-axis [4]. Moreover, on the basis of color Doppler myocardial imaging, 1D regional strain and strain rate (SR) curves can be calculated by comparing local myocardial velocity profiles. Strain and SR quantifies the actual deformation of the myocardium (expressed as a percentage) in systole and diastole [5].

The TDI SR imaging is prone to measurement error due to signal noise, acoustic artifacts and angle dependency. This may limit the application of TDI in routine clinical practice. Newer techniques, such as ‘speckle tracking’ algorithms, might be less vulnerable to measurement errors. Indeed, in contrast to TDI parameters, speckle tracking is an angle-independent technique as the movement of speckles in 2D grayscale images can be followed in any direction. The 2D technique provides comparable results to TDI for longitudinal strain, but offers a more user-friendly approach.

LV diastolic dysfunction
Measurements of diastolic function
Diastolic dysfunction refers to a condition in which abnormalities in LV function are present during diastole. The gold standard for assessing diastolic function remains the LV pressure–volume relationship, but this requires an invasive approach. Conventional echocardiography together with Doppler measurements of transmural and pulmonary veins flows, and the TDI mitral annular velocities created the possibility of noninvasively evaluating diastolic function and filling properties [6]. However, these techniques are complex and no single measurement on its own reflects diastolic function. Thus, a comprehensive assessment of a number of variables is required to evaluate diastolic function as correctly as possible [7].

Slowing and prolongation of LV relaxation becomes apparent at an early stage of LV diastolic dysfunction, because this part of the cardiac cycle is metabolically demanding. Impaired myocardial relaxation is characterized by decreased early, but enhanced atrial LV filling as well as less vigorous mitral annulus motion during early diastole compared to late diastolic motion. Thus, lower transmitral ratio of peak early filling (E) to peak atrial filling (A) and lower mitral annular early:late diastolic (E:A’ ) velocity ratios along with the prolongation of isovolumetric relaxation time might reflect impaired myocardial relaxation. Studies in the general population [8,9] demonstrated that LV relaxation, as reflected by these indices, substantially decreased with age not only in the whole study sample, but also in a selected healthy reference population (Figure 1). Current guidelines propose criteria to diagnose diastolic dysfunction that are not standardized for age [1,6]. It is likely that by ignoring age and by applying the same threshold values for the Doppler indexes throughout the age range, one may underestimate the prevalence of subclinical diastolic dysfunction (impaired relaxation), especially in young subjects with risk factors, such as hypertension, obesity and diabetes (Figure 2A & B).

The Doppler blood flow measurements and the TDI mitral annulus velocities can reflect abnormal LV relaxation as well as elevated LV filling pressure, another feature of LV diastolic dysfunction. Combining transmural flow velocity with annular velocity (E:E’ ratio) might be a tool for estimating LV diastolic dysfunction. Combining transmural flow velocity with annular velocity (E:E’ ratio) might be a tool for estimating LV diastolic dysfunction. In our population study, the 97.5th percentile of E:E’ ratio in the healthy reference subgroup was 8.4 [9]. In previous invasive studies, an E:E’ under 8 and E:E’ over 15 accurately indicated normal and elevated LV end-diastolic filling pressure, respectively [10]. However, the majority of patients with elevated LV end-diastolic filling pressure in the presence of normal EF (>50%), as inversely determined in several previous studies from pressure-volume loops, had an E:E’ ratio between 8 and 15 [10,12]. Ommen et al. suggested that an accurate prediction of LV filling pressures for an individual patient requires further characterization of the intermediate E:E’ group, for instance by measurement of blood flow in the pulmonary vein and left atrial (LA) volume [10].

Left atrial enlargement reflects chronic exposure to increased LV filling pressure, and it may serve as an integrative, easily obtainable measure of diastolic dysfunction [13]. Molecular mechanisms responsible for LA wall remodeling in patients with/ or at risk of HF have not yet been examined. The loss of LA mechanical function, as for instance occurs with the onset of atrial fibrillation, frequently triggers cardiac decompensation. Studies examining atrial function in patients with symptomatic diastolic HF recently confirmed the presence of reduced LA systolic function, particularly under stress conditions [14].

Prevalence & determinants of diastolic dysfunction in a general population
Presently, only few population studies [9,15,16] described the prevalence of preclinical LV diastolic dysfunction, using the new TDI indices along with classical pulsed-wave Doppler velocities. These studies applied a comprehensive Doppler analysis to grade LV
diastolic dysfunction in older adults (aged 60–86 years) [15], in subjects aged 45 years or older [16], or in the general population (aged 17–89 years) [9]. The reported prevalence of diastolic dysfunction in these studies [9,15,16] varied from 27.3 to 34.7%, and was influenced by a number of factors, including the characteristics of the population studied, and the criteria applied to diagnose LV diastolic dysfunction. The prevalence of diastolic dysfunction increased with age (Figure 3 & Table 1), but depended on applied arbitrary cut-off levels. Moreover, the risk of diastolic dysfunction increased significantly and independently with higher BMI, heart rate, systolic blood pressure, serum insulin and creatinine (Figure 3) [9]. Women were more at risk than men (Figure 3). In a cross-sectional study of participants of the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO), approximately 50% of hypertensive subjects had impairment of LV diastolic function, whereas only 12% of normotensive subjects could be classified as having abnormalities of LV diastolic function [9].

**Prognostic significance of LV diastolic dysfunction**

Recent clinical and community-based studies explored the prognostic role of classical Doppler and the new TDI-derived indices. Transmitial E:A ratio and mitral annular E’ velocity as well as E:E’ ratio had an independent prognostic value in patients with overt HF [17,18], hypertension [19] or myocardial infarction [20]. Population-based studies are essential to investigate the natural history of subclinical diastolic LV dysfunction and to determine its prognostic significance.

The Olmsted study [16] described the predictive significance of preclinical LV diastolic dysfunction, using the comprehensive approach of combining new TDI indexes along with classical transmitial Doppler velocities. In multivariable-adjusted analyses while controlling for age, sex and EF, mild diastolic dysfunction (hazard ratio: 8.31; p < 0.001), and moderate or severe diastolic dysfunction (hazard ratio: 10.17; p < 0.001) predicted all-cause mortality. However, in this study, the authors did not adjust the models for other important cardiovascular risk factors, such as systolic blood pressure, BMI, serum creatinine and total cholesterol. The Copenhagen City Heart Study [21] explored the isolated prognostic impact of the new TDI indices such as E’ and A’ velocities, and the E’:A’ and E:E’ ratios. In 1036 participants enrolled in the study, low systolic (S’) and A’ velocities derived from color Doppler imaging and averaged from 16 myocardial segments independently predicted total mortality [22]. The authors did not report transmitial velocities and did not explore whether the new TDI indexes captured prognostic information over and beyond classical Doppler measurements of diastolic function.

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**Figure 1. Age-specific percentiles of the E:A (A) and E:E’ (B) for the healthy reference sample (n = 239).**

A: Atrial mitral inflow; E: Early mitral inflow; E’: Early diastolic annular velocity.

Data from [9].
LV systolic dysfunction

Left ventricular systolic dysfunction was initially quantified by contrast cineventriculography, using EF before the introduction of echocardiography. Traditionally, EF measurement is used to diagnose HF. The view that systolic function is entirely normal in subjects with clinically overt HF and normal EF has been challenged [22]. The majority of these patients have a history of hypertension, diabetes and kidney dysfunction. Using the novel echocardiographic technique, one can also evaluate how the geometric and functional adaptation of the LV to increased cardiac load differs among patients. Patients with hypertension usually present with concentric remodeling (increased relative wall thickness despite normal LV mass) or eccentric LV hypertrophy (an increase in both relative wall thickness and LV mass), but have a normal-sized LV chamber and normal EF, even in the presence of a reduced longitudinal systolic function [23]. Indeed, in the FLEMENGHO study, strain and SR imaging enabled the detection of abnormalities in LV longitudinal function in subjects with LV remodeling but with normal EF [24]. Longitudinal and radial strain and SR significantly and independently decreased with age and relative wall thickness as measures of LV concentric remodeling [24]. By contrast, as expected, EF increased with age and relative wall thickness. Previous studies with radionuclide methods [25] or echocardiography [26] showed that in healthy subjects, LV EF at rest does not change, or increases even slightly with age, possibly due to the age-related increases in LV wall thickness. In keeping with our observations [24], studies applying TDI [27] or MRI [28] revealed that longitudinal shortening and/or radial myocardial thickening was lower in patients with LV hypertrophy and normal EF than in normal controls. Patients with LV hypertrophy have increased myocardial fibrosis, particularly in the subendocardium [29]. The contraction of the myocardial layer, which is located in the subendocardium, is mainly responsible for longitudinal shortening [30]. Thus, the decreased longitudinal deformation in subjects with LV concentric remodeling may be related to subendocardial fibrosis. Early subclinical changes in systolic function can be more readily detected in the LV basal segments, because the gradient of average wall stress increases from the apex to the base [31]. A recent study in hypertensive patients [32] showed that the basal septal strain correlated inversely with mean arterial pressure and basal septal wall thickness. Thus, LV strain and SR are sensitive tools in the detection of subclinical systolic dysfunction associated with LV remodeling.

In a healthy reference group (n = 236) enrolled in the FLEMENGHO study [24], the 5th percentiles were considered as the lower limits of normality for the averaged longitudinal and radial strain in the LV basal segments. Absolute values for normal myocardial deformation should be higher than 18.5 and 44.5% for longitudinal and radial strain. The prevalence of subclinical LV systolic dysfunction in hypertensive subjects, as estimated from longitudinal and radial strain measurements, was as high as 19% [24].

The major limitation of TDI in the assessment of LV function is the dependency on the angle of the ultrasound beam and the difficulties in assessing regional LV torsional movement. The rotational component of cardiac contraction plays a significant role in LV ejection and early diastolic LV filling, but it is poorly imaged by most TDI techniques. Newer techniques, such as 'speckle tracking' algorithms, involve identification of multiple unique patterns of echocardiographic pixel intensity that are automatically tracked throughout the cardiac cycle. Each pixel’s angular displacement is averaged to provide a measurement of both degree and direction of rotational motion for each segment of the myocardium. This method is not limited by angle dependency and compares favorably with MRI. A recent study in hypertensive patients with HF [33] showed that the speckle tracking technique, by providing the combined assessment of LV longitudinal, radial and circumferential function, is a promising tool in the diagnosis of systolic LV dysfunction in hypertension.

**Expert commentary**

In contrast to HF with reduced EF, where events (e.g., myocardial infarction) often signal the onset of cardiac dysfunction and symptoms, this is not the case in HF with normal EF, which starts silently. Conventional echocardiography combined

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**Table 1. Age distribution of the total and healthy reference samples, and by diastolic function group.**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy reference population</td>
<td>55 (10.2)</td>
<td>49 (9.1)</td>
<td>131 (24.3)</td>
<td>131 (24.3)</td>
<td>99 (18.4)</td>
<td>74 (13.7)</td>
</tr>
<tr>
<td>Normal function</td>
<td>45 (18.8)</td>
<td>36 (15.1)</td>
<td>81 (33.9)</td>
<td>53 (22.2)</td>
<td>19 (7.9)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Group 1 – Impaired relaxation</td>
<td>52 (13.3)</td>
<td>47 (12.0)</td>
<td>120 (30.6)</td>
<td>104 (26.5)</td>
<td>52 (13.3)</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>Group 2 – Elevated end-diastolic pressure</td>
<td>3 (5.7)</td>
<td>1 (1.9)</td>
<td>7 (13.2)</td>
<td>17 (32.1)</td>
<td>13 (24.5)</td>
<td>12 (22.6)</td>
</tr>
<tr>
<td>Group 3 – Severely impaired relaxation</td>
<td>1 (1.3)</td>
<td>3 (3.9)</td>
<td>8 (10.5)</td>
<td>27 (35.5)</td>
<td>37 (48.7)</td>
<td>4 (4.4)</td>
</tr>
</tbody>
</table>

Values are number of subjects (%). Impaired relaxation (group 1) indicates low age-specific E:A and normal E:E'; elevated end-diastolic pressure (group 2) indicates normal age-specific E:A and high E:E'; and confirmed by the differences in durations between the mitral atrial flow and the reverse pulmonary vein flow during atrial systole; severely impaired relaxation (group 3) indicates low age-specific E:A and high E:E'.

Data from [9].
Review

with TDI and speckle tracking techniques is a sensitive tool to assess early subclinical changes in systolic and diastolic LV function. Impairment of LV diastolic as well as systolic function appears very early in the course of heart disease. Because systole and diastole are active and complementary components of the cardiac cycle, they are both contributing to overall myocardial

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**Figure 2. Examples of different patterns of diastolic function as assessed by transmitral Doppler and mitral annular TDI velocities.**

(A) 61-year old women with a normal age-specific transmitral E:A ratio (from 2.5th to 97.5th percentiles of the reference subgroup, Figure 1) and without evidence of increased LV filling pressures (E:E’ = 7.4). (B) 60-year old man with an abnormally low age-specific transmitral E:A ratio (0.62) indicative of impaired relaxation (less than 2.5th percentile of the reference subgroup), but without evidence of increased LV filling pressures (E:E’ = 7.5). (C) 68-year old women who had moderately elevated end-diastolic filling pressure (E:E’ = 16.7), but E:A ratio within the normal age-specific range (from 2.5th to 97.5th percentiles of the reference subgroup). (D) 54-year old women with an elevated E:E’ ratio (15.2) and an abnormally low age-specific E:A (0.70).

A: Atrial mitral inflow; A’: Late diastolic annular velocity; E: Early mitral inflow; E’: Early diastolic annular velocity; LV: Left ventricular; TDI: Tissue Doppler imaging.

Data from [9].
performance. LV systolic and diastolic dysfunction coexists to varying degrees. Studies based on representative random population samples provide a wide spectrum of different stages of HF and LV dysfunction in subjects who are usually untreated. Studies in patients are informative, but have the disadvantage of selection bias, small sample sizes and being confounded by treatment. Recent community-based studies revealed a higher than hitherto expected prevalence of LV systolic and diastolic dysfunction, using the new echocardiographic imaging technique. Future prospective studies should further clarify the prognosis associated with early symptom-free LV dysfunction. Along similar lines, existing imaging techniques have not been adequately validated in terms of disease progression or the prediction of morbidity and mortality. Moreover, easily applicable screening algorithms including imaging indexes and biomarkers for the early detection of asymptomatic stages of the disease are lacking. Current ‘state-of-the-art’ management of subclinical LV dysfunction relies only on the control of risk factors, such as hypertension, diabetes and kidney dysfunction.

Five-year view

The natural history of subclinical systolic and diastolic LV dysfunction in the general population is currently unknown. Serial imaging studies are required to clarify the progression of LV changes from stage A to stage B and later onto stage C, as previously carried out in a series of patients with ischemic heart disease after myocardial infarction. Further studies should quantify the incidence of LV diastolic dysfunction, its relation in time with subclinical LV systolic dysfunction or vice versa, and the prognosis associated with early symptom-free LV dysfunction. Experts in the field repeatedly underscored that this issue is a top research priority. Along similar lines, it remains unknown to what extent the new sophisticated echocardiographic indices, such as LV strain, SR and LV torsion might contribute to the stratification of cardiovascular risk in the general population.

Risk factors for HF, such as hypertension and diabetes mellitus, also predispose to vascular complications, such as myocardial infarction and stroke. Stiffening of the large arteries is a common feature of aging, leads to isolated systolic hypertension, and is exacerbated by many common disorders, such as hypertension and diabetes mellitus. The heart typically adapts to confront higher and later systolic loads by both hypertrophy and LV stiffening. Increased vascular loading on the heart likely contributes to LV dysfunction. Ventricular–arterial coupling disease has to be further explored in subjects with subclinical LV dysfunction as well as in the general population.

A panel of biomarkers that could be measured in blood and urine reflecting different morphological and functional LV characteristics might constitute a great leap forward in the diagnosis of subclinical LV dysfunction, but still needs to be validated. Finally, the question of whether genetic risk factors for LF dysfunction might be identified and whether the principle of genetic randomization, when applied to the aforementioned biomarkers, might be helpful in establishing a causal association between the disease and the marker has to be addressed.
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Key issues

- Heart failure (HF) is growing into a major health problem.
- HF guidelines place special emphasis on the detection of subclinical left ventricular (LV) systolic and diastolic dysfunction and the timely identification of risk factors for HF.
- Impairment of LV diastolic as well as systolic function appears very early in the course of heart disease.
- Identification of patients with subclinical LV dysfunction is important for early diagnosis and intervention.
- Echocardiography is a sensitive tool to detect early subclinical changes in LV function.
- Community-based studies revealed a higher than hitherto expected prevalence of LV systolic and diastolic dysfunction, using the new echocardiographic imaging technique.
- Future prospective studies should further clarify the prognosis associated with early symptom-free LV dysfunction.

References

Papers of special note have been highlighted as:

• of interest
•• of considerable interest

•• Represents an effort by the Heart Failure and Echocardiography Associations of the European Society of Cardiology to state the essential points on the diagnosis of heart failure with normal ejection fraction.

• Provides prevalence estimates and prognostic validation for heart failure (HF) staging in a community.

• Reviews the role of echocardiography in HF and its prognostic value and discusses promising future techniques for echocardiographic-based imaging in HF.

• Described a technique for imaging the velocities of tissue motion within the myocardium.

• Described the technique for echocardiographic evaluation of strain and strain rate measurements.

• Underscored that a comprehensive assessment of a number of echocardiographic variables is required to evaluate diastolic function as correctly as possible.

• Provides a consensus statement on the diagnosis of diastolic heart failure.

• Described the overall prevalence and determinants of left ventricular (LV) diastolic dysfunction in a random sample of a general population (aged 17–89 years). The study also described one of the categories of diastolic dysfunction as having a low transmitral early:atrial mitral inflow (E:A) ratio (indication of impaired myocardial relaxation) but an elevated E:early diastolic annular velocity (E’) ratio. This was a heretofore undescribed group of patients.

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15 Abhayaratna W, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the...
with age, body weight, central obesity and relative wall thickness.


Website


www.acc.org/qualityandscience/clinical/topic/topic.htm

- The American Heart Association and American College of Cardiology proposed the concept of heart failure staging to emphasize the progression from HF risk factors to asymptomatic cardiac dysfunction to clinically overt HF.

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- The Olmsted study described the predictive significance of preclinical LV diastolic dysfunction, using the comprehensive approach of combining the new tissue Doppler imaging indices along with classical transmitral Doppler velocities.


- Explored the early signs of LV systolic dysfunction in a general population, using tissue Doppler imaging technique. Left ventricular strain and strain rate decrease