Current Perspectives on Cardiac Function in Patients With Diastolic Heart Failure

Jianwen Wang, MD, PhD; Sherif F. Nagueh, MD

Despite recent advances in the diagnosis and management of heart failure, the rate of hospitalizations for this condition is increasing. At least 50% of patients present with heart failure despite a normal ejection fraction (EF) and are referred to as having heart failure with normal EF or diastolic heart failure (DHF). Recently, a group of investigators met to address the issue of nomenclature and agreed that the term DHF is preferred but that it does not refute the presence of other abnormalities in this condition. We therefore use this term throughout the present review.

There are several opinions about the pathophysiology of this condition that have been expressed passionately by many groups. They include issues pertaining to left ventricular (LV) systolic properties, ventricular arterial coupling, and last but not least, LV diastolic function. Recent studies that used novel imaging modalities and others that used conductance catheters in DHF patients have provided additional data that are pertinent to the ongoing debate and have potential therapeutic implications. However, before discussing the recent studies, it is important to comment on certain morphological characteristics in DHF patients that are distinct from those in patients with systolic heart failure. In particular, LV dimensions and volumes are normal in DHF patients, whereas wall thickness and LV mass are increased, although the latter finding is not universal. In an exception to the above findings, a recent study reported that LV end-diastolic volumes were increased in DHF patients. However, a single M-mode measurement was used to convert LV dimensions to volumes, only 51% of the original sample size was included, and 90% of DHF patients had normal LV volumes, with only 10% showing LV dilatation. In light of the above, it is reasonable to conclude that LV volumes are normal in most DHF patients. The most recent set of criteria for diagnosing DHF by the European Society of Cardiology recognize the presence of an EF >45% and a LV end-diastolic volume index <97 mL/m² as 1 of 3 essential criteria to establish this diagnosis. The other 2 criteria are signs and symptoms of heart failure and abnormalities in LV diastolic function/filling. Notwithstanding the need for uniformly accepted definitions, a number of disease processes result in DHF and affect cardiac function in such a way that there can be different pathophysiological changes, depending on the population studied. We devote this review to 3 fundamental aspects of cardiac function in DHF: systolic properties, ventricular-arterial coupling, and diastolic function.

LV Systolic Function

A recent review addressed this topic and concluded that systolic function is normal in DHF patients and that regional myocardial velocity measurements are limited in accuracy because they are subject to tethering and translation. The authors favored the use of myocardial deformation to address this question. Our review examines studies that used deformation and twist mechanics in DHF patients and then addresses questions on contractile reserve in DHF.

Myocardial Strain

Technical Aspects

In single-myocyte experiments, myocyte shortening and lengthening can be measured while being stimulated under microscopy. Although deformation can be measured by sonomicrometry or radiopaque markers, noninvasive methods are the most practical approach and are used in patients. Strain is defined as the relative change in myocardial length, and the rate of deformation is referred to as strain rate (SR; in seconds⁻¹). Depending on the direction of deformation, longitudinal, circumferential, and radial deformation can be measured. However, from the perspective of the heart, deformation occurs not only perpendicular to a given plane (normal strain) but also in between planes, or shear strain. Mathematically, strain is the integral of SR, with compression expressed in a negative value and expansion in a positive value.

Myocardial tagging can quantify regional deformation by cardiac magnetic resonance (MR) and is regarded as the gold standard. In addition, both strain and SR can now be measured with echocardiographic techniques, tissue Doppler (TD), and 2-dimensional speckle tracking, and both were validated against sonomicrometry and cardiac MR. Importantly, echocardiographic methods have a higher frame rate than cardiac MR and are better suited to study temporal aspects of cardiac function. For TD, SR is measured as the myocardial velocity gradient. The TD-based method (Figure 1) is subject to reverberation artifacts, is angle dependent, and...
drift (strain curve does not return to same value from beat to beat). Given these limitations, along with lower reproducibility, the widespread clinical use of this technology was met with little enthusiasm. Speckle tracking is based on the recognition and tracking of speckles, which represent unique acoustic identification for each myocardial region, recognized by the pattern of gray values. This method is not angle dependent, is more reproducible than TD, and can be used to determine circumferential strain, in addition to radial and longitudinal strain (Figure 2). However, speckle tracking has a lower frame rate than TD and can lead to an underestimation of deformation rate measurements.

Clinical Studies
Several groups have described reduced systolic myocardial velocities in the longitudinal plane using TD. Furthermore, some advocate the concept that there is a continuum whereby systolic function is progressively depressed as patients proceed from hypertensive LV hypertrophy to DHF. Since then, a number of studies have used systolic strain/SR to draw inferences on cardiac function in patients with diabetes, obesity, and hypertension. Most of these studies reported abnormalities in systolic strain and SR compared with normal control subjects. However, it is not known whether patients with these diseases will progress to DHF or develop a depressed EF on follow-up.

One study directly examined myocardial function in DHF patients using strain measurements by speckle tracking. Global strain was computed from all myocardial segments in the longitudinal, circumferential, and radial directions, and DHF was diagnosed using clinical criteria, normal LV EF and volumes, and increased mean wedge pressure (>12 mm Hg). Because strain is affected by preload, afterload, and intrinsic myocardial contractility, meridional and circumferential systolic wall stress was computed and compared between DHF patients and the control group. Despite similar systolic stress and end-diastolic volume, longitudinal and radial strains were significantly lower in DHF patients compared with control subjects (Figure 2), but circumferential strain was normal. However, all strain measurements in DHF patients were significantly higher compared with patients with heart failure and depressed EF. The study was limited by small sample size and differences in age and heart rate between the patient groups.

DHF patients may have abnormal systolic function for several reasons. They include the presence of hypertension, obesity, and diabetes mellitus, which can lead to LV macrovascular and microvascular abnormalities, interstitial fibrosis, and an intrinsic depression of myocardial contractility. In that regard, we have shown that myocardial velocity and strain are significantly related to interstitial fibrosis. Furthermore, one can speculate that the extent of pathology and/or abnormal function is limited to subendocardial fibers in DHF, so the subepicardial fibers that account for circumferential strain are spared. The presence of systolic dyssynchrony is another reason, as discussed in the following sections.

In conclusion, the new data support the view that myocardial deformation is depressed in some patients with DHF, although individual variations exist and some patients can have normal values.
LV Twist

During systole, the LV base and apex rotate in opposite
directions. Major rotation occurs during the ejection phase,
with the apex rotating in a counterclockwise direction (Figure
3, Movie I in the online Data Supplement) and the base
rotating in a clockwise direction (Figure 4, Movie II). The net
difference, LV twist, is expressed in degrees. To account for
LV size, the net degree of rotation is divided by LV long axis
and is called torsion (in degrees per centimeter). Until
recently, torsion was obtained by cardiac MR, but now it can
be acquired by echocardiography, which has higher feasibil-
ity and temporal resolution.

Technical Aspects

Torsion can be measured by TD and speckle tracking.
However, given the angle independence of speckle tracking
and its higher reproducibility, this technique is preferred for
measuring rotation. LV twist mechanics has been validated
against sonomicrometry and cardiac MR. Nevertheless,
attention to the cross-sectional planes and the overall techni-
cal quality of the study is essential to obtaining accurate
values. Erroneous measurements can occur with poor defini-
tion of LV apex or base and through plane translation, echo
dropouts, and reverberations.

Physiological Aspects

The helical arrangement of LV subendocardial and subepi-
cardial fibers accounts for twist. The subendocardial myo-
cardial fibers are oriented as a right-handed helix; the
subepicardial fibers are arranged as a left-handed helix.
Because of the larger radius of the subepicardial fibers, these
fibers are the dominant force for rotation. Therefore, when
viewed from the apex, apical rotation occurs in a counter-
clockwise direction. The subendocardial torque counteracts
this rotation. Structural/functional changes influencing either
subendocardial and/or subepicardial fibers result in an imbal-
ance between the 2 helical torques and a change in twist.
Animal and human studies have shown the impact of load and
LV contractility on twist. An acute increase in preload leads
to a decrease in twist, whereas a decrease in afterload leads to
an increase in twist. An increase in LV contractility is
accompanied by an increase in apical rotation and twist.

Figure 2. Examples of twist (row 1), circumferential strain (Sl; row 2), longitudinal strain (Sl; row 3), and radial strain (Sl; row 4) from a
control subject (left), a patient with DHF (middle), and a patient with systolic heart failure (SHF; right). The traces shown for radial strain
were obtained from each of the 6 myocardial segments at the papillary muscle short-axis level, with the average strain shown in heavy
blue and arrows. Notice the presence of normal twist and circumferential strain in DHF but lower longitudinal and radial strain com-
pared with the control subject. Reprinted from Wang et al., with permission from Oxford University Press and the European Society of
Cardiology.
The complex interplay between all of these factors determines twist values in DHF.\textsuperscript{10}

**Clinical Studies**

Few studies\textsuperscript{10,19,20} have evaluated torsional mechanics in patients with LV hypertrophy and normal EF (the Table). In 1 study,\textsuperscript{19} LV torsion was normal in patients with hypertrophy, without intergroup differences based on its extent. In another,\textsuperscript{20} LV twist was increased in patients with early diastolic dysfunction and normal in patients with advanced grades. These results are similar to observations in patients with aortic stenosis using cardiac MR\textsuperscript{21,22} and in patients with type 1 diabetes and tight glycemic control.\textsuperscript{23}

For DHF, both peak twist and twisting rate (Figure 2) were preserved and similar to those in a normal control group.\textsuperscript{10} The above results may be explained by abnormally depressed subendocardial function in DHF patients resulting from ischemia and/or fibrosis.\textsuperscript{24,25} Accordingly, the subepicardial torque is unopposed, leading to normal/increased twist values. We noted that circumferential strain and LV twist were the independent predictors of LV EF in a group of DHF patients, and it is possible that normal twist is a compensatory mechanism in DHF that can help maintain a normal EF.\textsuperscript{10}

**Systolic Dyssynchrony**

The issue of mechanical dyssynchrony was examined in DHF.\textsuperscript{26–28} TD was used to assess dyssynchrony, and DHF patients were compared against a normal control group and against patients with heart failure caused by depressed EF using methods similar to those applied to patients with depressed EF (time from QRS to peak systolic velocity). In 1 report,\textsuperscript{26} the maximal time delay between 4 basal segments (septal, lateral, anterior, and inferior) was derived; in the other, the SD from 12 segments or the Yu et al\textsuperscript{27} method was calculated. The prevalence of systolic dyssynchrony in DHF was similar in 2 of the 3 studies (33% versus 39%), with weak correlation between QRS duration and systolic time delay.\textsuperscript{26,27} Importantly, in DHF patients with systolic dyssynchrony,\textsuperscript{26} LV systolic performance was reduced (reduced stroke work), as were LV systolic function (reduced EF and reduced slope of stroke work versus end-diastolic volume; Figure 5) and myocardial contractility (inferred from relationship between midwall fractional shortening and circumferential wall stress; Figure 6). A number of previous studies reported abnormal myocardial function in roughly a third of the patients with LV hypertrophy and DHF,\textsuperscript{5} and systolic dyssynchrony can explain the previous observations.

An interesting investigation\textsuperscript{28} reported on the difference in systolic dyssynchrony between patients with hypertension and diastolic dysfunction (n=26) and DHF patients (n=13). The investigators assessed dyssynchrony by the Yu et al\textsuperscript{27} method at rest and during stress, which can be challenging and mandates close attention to high frame rates for reliable measurements. At rest, the dyssynchrony index was signifi-
cantly greater in both patient groups than in the control group, but there was no significant difference between the 2 patient groups. The 6-minute treadmill exercise test led to deterioration in dyssynchrony only in the DHF patients and was associated with higher plasma N-terminal pro-brain natriuretic peptid levels, implicating dynamic dyssynchrony in the development of DHF symptoms.

**Ventricular-Arterial Coupling**

Effective arterial elastance (E_A) approximates the arterial afterload faced by the LV during systole. It can be estimated noninvasively as LV end-systolic pressure/stroke volume (mm Hg/mL), where LV end-systolic pressure is derived as 0.9\(\times\)systolic blood pressure and stroke volume is calculated by echocardiography. E_A is affected by the peripheral vascular resistance, arterial compliance, and cardiac cycle durations. The normal resting value of E_A is 2.2\(\pm\)0.8 mm Hg/mL.

LV end-systolic elastance (E_LV in mm Hg/mL) is an index of contractility that is load independent. It is determined invasively as follows: E_LV=LV end-systolic pressure/(end systolic volume−V_0), where V_0 represents the volume (x axis) intercept of the end-systolic pressure-volume relationship. The noninvasive calculation is possible by 2 methods. In 1 method, V_0 is ignored (V_0 is less than end-systolic volume), ie, LV end-systolic pressure/end systolic volume. In the other, systolic and diastolic blood pressures, EF, stroke volume, preejection, and ejection periods are needed. Its normal resting value is 2.3\(\pm\)1 mm Hg/mL. Therefore, the E_A/E_LV ratio is normally 1.0\(\pm\)0.36. E_LV and E_A increase proportionately with age in normal men, and their ratio remains unchanged. Normal women show a higher increase in E_LV with age, so the ratio decreases slightly.

In hypertensive men, E_A and E_LV are greater than in normal control subject, but their ratio remains normal. Hypertensive women develop a disproportionately greater increase in E_LV, so their ratio is significantly lower than normal subjects. In patients with systolic heart failure, E_A increases as a result of increased peripheral vascular resistance, whereas E_LV is decreased. Thus, the E_A/E_LV ratio increases with reduced myocardial efficiency. In DHF, both E_A and E_LV increase, and in 3 studies, the E_A/E_LV ratio was similar in DHF patients compared with those with hypertension but not heart failure. Therefore, the consensus from the published literature supports the notion that abnormal ventricular-arterial coupling at rest is not the culprit for developing DHF. However, 1 study noted a reduced vasodilator reserve with exercise; additional data are needed during exercise for reliable conclusions.

**Table. Summary of Observational Studies With Twist/Untwist Measurements in Patients With Normal EF**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age, y</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeuchi et al</td>
<td>49</td>
<td>63±11</td>
<td>Medically controlled hypertension, not in heart failure</td>
<td>Twist similar to normal volunteers, but untwisting rate during isovolumic relaxation period significantly reduced and delayed</td>
</tr>
<tr>
<td>Park et al</td>
<td>116</td>
<td>~57.6±15</td>
<td>Hypertension in 26 patients</td>
<td>Twist and untwisting rate significantly higher in stage I diastolic dysfunction but similar to control subjects in stages II and III</td>
</tr>
<tr>
<td>Wang et al</td>
<td>20</td>
<td>63±16</td>
<td>DHF</td>
<td>Twist and twisting and untwisting rates similar between DHF patients and control subjects</td>
</tr>
</tbody>
</table>

**Figure 5.** Relation between LV end-diastolic volume (EDV) and stroke work (SW). The relation in the control group is shown by the solid line and solid circles; in patients with DHF and systolic dyssynchrony, by the dotted line and open circles; and in patients with DHF but without systolic dyssynchrony, by the dashed line and solid squares. DHF patients without systolic dyssynchrony and the control group had similar linear relationships. This relationship was shifted downward in DHF patients with systolic dyssynchrony. Reprinted from Wang et al, with permission from Elsevier. Copyright 2007, American College of Cardiology.

**Figure 6.** Relation between midwall fraction shortening and circumferential wall stress. Patients with DHF and systolic dyssynchrony are shown by open circles; patients with DHF but without dyssynchrony, by solid circles. The data points for patients with systolic dyssynchrony were outside the lower 95% prediction interval for the control group. Reprinted from Wang et al, with permission from Elsevier. Copyright 2007, American College of Cardiology.
Contractile Reserve

Very few studies addressed the important question of contractile reserve in DHF. A recent study measured $E_{LV}$ in 70 DHF patients at rest, with hand grip, and with atrial pacing to a heart rate of 120 bpm. The investigators noted that pacing resulted in an increase in $dP/dt$ and $E_{LV}$ in DHF that was similar to a normal group, but DHF patients developed a significant decrease in LV end-diastolic volume and stroke volume. A smaller study enrolled DHF patients, but not normal control subjects, and assessed the force-frequency volume. A smaller study enrolled DHF patients, but not normal control subjects, and assessed the force-frequency relation using rapid atrial pacing. Both $E_{LV}$ and $dP/dt$ by conductance catheters were increased in DHF.

During hand grip, the increment in heart rate was significantly less in DHF patients than in the control group, but LV end-diastolic volume did not change significantly in patients or control subjects.

Pacing and hand grip do not directly measure changes in cardiovascular function with exercise. This question was raised in 7 DHF patients with markedly limited exercise tolerance as a result of a reduced LV end-diastolic volume and stroke volume with exercise (as would be inferred from the Frank-Starling mechanism), along with a large increase in mean wedge pressure but with a preserved EF, indicating that increased LV diastolic stiffness rather than systolic dysfunction accounted for exercise limitation. Recently, investigators examined 17 DHF patients at rest and during upright ergometry with radionuclide ventriculographic imaging and compared rest and exercise cardiovascular function with that of 19 patients matched for age, gender, and comorbidities. Cardiovascular function at baseline was similar between the 2 groups, but DHF patients had a significantly worse exercise tolerance, along with a 40% lower increment in heart rate, lower cardiac output, and less vasodilation, raising questions about abnormal autonomic function in DHF.

From the above-mentioned studies, it appears that the force-frequency relationship is preserved in DHF when assessed by atrial pacing. However, the chronotropic response to hand grip and upright exercise is depressed in DHF, but additional studies are clearly needed in more patients.

LV Diastolic Function

The existing guidelines recognize the need to document abnormal diastolic function to establish the diagnosis of DHF. However, studies using direct hemodynamic measurements have found contradictory results with regard to the presence of increased stiffness and impaired relaxation in DHF. The invasive approach is impractical for establishing the diagnosis of DHF, and noninvasive assessment is preferred. Here, we comment on recent imaging studies that evaluated new diagnostic modalities in this population and on reports that provided mechanistic insights into the abnormalities in LV diastolic function in DHF patients, including studies that assessed the diastolic reserve.

Established Methods

Increased lung uptake of radioactive isotopes during a stress perfusion study is indirect evidence of increased LV filling pressures but is limited by radiation exposure and low sensitivity. Likewise, MR imaging (MRI) can be used to estimate LV filling pressures, but only 1 such study has been published, and MRI has high costs and relatively limited availability. Echocardiography has by far the highest feasibility and most evidence for noninvasive assessment of diastolic function.

In DHF, the ratio of mitral E velocity to mitral annulus $e'$ velocity provides a good assessment of LV filling pressures, and the lateral E/e' ratio appears most accurate. When the E/e' ratio (septal, lateral, average) is $\geq 8$, LV filling pressures are usually $<15$ mm Hg. A septal ratio $\geq 15$, a lateral ratio $\geq 12$, and an average ratio $\geq 13$ indicate filling pressures $>15$ mm Hg. However, the overall performance of E/e' leaves room for improvement, particularly in patients with intermediate ratios. Therefore, one should evaluate left atrial (LA) volume index ($\geq 34$ mL/m$^2$), pulmonary artery systolic pressure ($>35$ mm Hg without pulmonary disease), the duration of the atrial reversal signal in pulmonary venous flow (duration $\geq 30$ ms longer that mitral A), the change in E/A ratio with Valsalva maneuver (decrease by $\geq 50$%), and the ratio between isovolumetric relaxation time (IVRT) and the time delay $(T_{E-e'})$ between onset of mitral E and annular $e'$ (IVRT/$T_{E-e'}$ ratio <2). The IVRT/$T_{E-e'}$ ratio has good accuracy in patients with normal EF, mitral valve disease, and equivocal values of E/e' and can help identify patients with constrictive pericarditis.

Novel Methods: Diastolic Strain Rate

A number of interesting reports were published that proposed diastolic SR for the assessment of LV relaxation. On a regional level, a delay in the onset of myocardial lengthening and postsystolic contraction identify ischemic segments. Furthermore, early diastolic SR relates well to regional diastolic stiffness in acute and chronic infarction animal models, although it is also related directly to LV end-diastolic pressure. Segmental early diastolic SR was inversely related to the extent of collagen deposition in the interstitial matrix, suggesting a potential role for detecting myocardial viability.

Reduced early diastolic SR is observed in DHF, and it is also related directly to LV end-diastolic pressure. With speckle tracking, it is possible to measure global longitudinal SR during IVRT (GSR$_{IVR}$) from the apical 4, 2, and long-axis views (Figure 8). GSR$_{IVR}$ has a number of advantages over established methods. It is acquired directly from LV myocardium, as opposed to indirect data of annulus and blood flow velocities. It is not affected by mitral annulus or valvular disease. It occurs during IVRT when valves are closed and therefore is not exposed to transmitral pressure gradient. It is derived from all myocardial segments and thus is a true global index. Finally, unlike velocity, it is not affected by translation and tethering and takes into consideration the initial resting length. In an animal study, GSR$_{IVR}$ related well with invasive indexes of LV relaxation and was not affected by preload, and similar relations were observed in patients (Figure 9). Importantly, the ratio of mitral E velocity to GSR$_{IVR}$ predicted filling pressures well in an initial group of 50 patients and a prospective group of 24 patients. It was most useful when the E/e' ratio was inconclusive and was more accurate than E/e' in patients with normal EF and those with regional dysfunction. Although promising, accurate
LV Suction

Physiological Aspects

During systole, LV contraction leads to the storage of potential energy, which, when released, provides the restoring force that aids LV filling. An increase in LV contractility leads to higher restoring forces and more effective suction. In addition to contractility, the elastic properties of the LV come into play and are determined by the giant myofilament protein titin, extracellular collagen (microscopic spring), and the helical arrangement of myocardial fibers (macroscopic springs). At the sarcomere level, elastic energy is stored in titin when the protein is compressed below its slack length. During diastole, titin springs back to release the stored energy. There are 2 titin isoforms in human myocardium: N2B and N2BA. The N2B isoform leads to higher cellular stiffness but greater restoring forces.55 The reversal of apical and basal rotation leads to untwisting. Therefore, untwisting can be of value in studies of LV diastolic function. MRI, TD, and speckle tracking echocardiography14 can be used to measure untwisting rate.

LV untwisting rate has been evaluated as an index of myocardial relaxation. In 1 study, 10 dogs underwent hemodynamic and MRI measurements at rest, during volume loading, and during dobutamine, esmolol, and methoxamine infusions.56 When data from all dogs were pooled and adjusted for individual variations, a strong relation (r²=0.85, P<0.0001) was observed between τ and untwisting rate.

In another animal model that used dobutamine and esmolol to alter LV inotropic and lusitropic states and inferior vena caval occlusion to alter LV preload, untwisting rate was measured by speckle tracking echocardiography with simultaneous hemodynamic measurements.57 In that model, dobutamine led to shortening of τ and an increase in untwisting rate, whereas esmolol had the opposite effect, with statistically significant differences between baseline, dobutamine, and esmolol stages. More important, vena caval occlusion induced significant changes in untwisting rate despite the absence of a significant change in τ regardless of whether baseline, dobutamine, or esmolol data sets were considered. Furthermore, untwisting rate tracked the changes in LV end-systolic volume best, to such an extent that it was almost identical in experimental settings with similar end-systolic volumes but widely different LV relaxation status (eg, esmolol with vena caval occlusion and baseline state in the absence of drugs). When all experimental stages were combined, a strong and inverse correlation (Figure 10) was observed between LV end-systolic volume and untwisting rate (r²=0.64, P<0.001). The timing of untwisting is affected by loading conditions; it is delayed with an acute increase in preload.16

Clinical Studies

Some investigators have shown that twist mechanics are normal in elderly individuals.58,59 Normally, untwisting begins in late systole and is completed before mitral valve opening. However, with systolic dysfunction, twist is reduced and recoil is delayed and reduced, which adversely affects LV filling.60 Few studies have been published on LV recoil in patients with normal EF (the Table). In a study19 that used...
speckle tracking, LV untwisting rate was reduced and delayed in 49 patients with LV hypertrophy and normal EF and was worst in patients with the most extensive hypertrophy. However, another study with speckle tracking noted that untwisting rate is increased with early-stage diastolic dysfunction and becomes normal with more advanced grades, except in patients with cardiac amyloidosis, in whom it was significantly reduced.20 We noticed that the LV untwisting rate is preserved in DHF patients as a group (Figure 11). Furthermore, LV untwisting rate related well to LV twist (direct correlation) and end-systolic volume (inverse correlation) regardless of LV EF.57 On the other hand, LV untwisting rate was significantly related to τ only in patients with depressed EF, not in patients with DHF. However, a subset of DHF patients had delayed onset and delayed peak of untwisting. These patients had larger LA volumes and higher pulmonary artery pressures,57 although the difference was not significant (P=0.07), probably because of the sample size.

In summary, the preserved twist and untwisting rate may compensate for impaired LV relaxation in DHF. LV untwisting rate should be assessed with respect to not only its peak value but also timing; if delayed, it does not support LV filling. Untwisting rate provides complementary information in that it represents a mechanistic link between contractility and diastolic suction and filling.

**Diastolic Dyssynchrony**

The concept of diastolic dyssynchrony and its contribution to diastolic dysfunction is well supported by a number of experimental and human studies.61,62 Most recently, it was examined in DHF studies in which clinical findings and invasive measurements were used to establish the diagnosis.26,27 Diastolic dyssynchrony was assessed from the time interval between the QRS complex and the onset/peak segmental early diastolic velocity, using the maximum time...
delay between 4 basal segments\(^26\) or the standard deviation from 12 segments.\(^27\) Both \(\tau\) and mean wedge pressure increased in parallel with the prolongation of the diastolic time delay.\(^26\) Interestingly, a strong direct relation was observed between LV mass and diastolic time delay,\(^26\) raising the possibility that regression of LV hypertrophy can lead to an improvement in LV relaxation through a reduction in diastolic dyssynchrony, although the short duration of the study (<2 weeks) precluded the evaluation of this hypothesis.

In addition, DHF patients were examined after treatment for heart failure with antihypertensive therapy, which led to a significant reduction in blood pressure and diastolic time delay.\(^26\) The improvement in diastolic dyssynchrony was closely coupled to the improvement in LV relaxation. These observations support the conclusion that increased afterload per se has an unfavorable effect on LV synchrony and that its reduction can lead to an improvement in LV relaxation, in part through the reduction in diastolic dyssynchrony.

**Diastolic Reserve**

Exercise results in an increase in LV stroke volume to meet the increased metabolic demands. Normally, this is achieved by increased cardiac contractility and enhanced LV suction and filling without an increase in filling pressures. Besides contractile reserve and arterial elastance (see above), DHF patients have limitations resulting from their diastolic dysfunction. It is therefore advantageous to assess LV diastolic function not only at rest but also during exercise. Invasive studies have shown that DHF patients have abnormalities in LV relaxation and stiffness that persist during the stress of tachycardia and hand grip when filling pressures rise significantly.\(^38,39\)

Noninvasive evaluation is based primarily on the assessment of LV volumes, mitral annulus e’ velocity, E/e’ ratio with exercise as a surrogate for LV filling pressures, and tricuspid regurgitation jet by continuous-wave Doppler (for estimating pulmonary artery systolic pressure) using supine bike echocardiography, which allows time for the adequate acquisition of 2-dimensional and Doppler data.\(^63\) In normal subjects, LV relaxation is enhanced with exercise, and e’ velocity increases in parallel with mitral E velocity, so the E/e’ ratio is unchanged. On the other hand, patients with diastolic dysfunction develop a much larger increase in mitral E velocity as a result of the elevated LA pressure, with a
smaller change in $e'$ (resulting from impaired LV relaxation). Accordingly, the $E/e'$ ratio increases with exercise in DHF patients, as does the estimated pulmonary artery systolic pressure. Invasive studies validated the $E/e'$ ratio acquired during exercise against LV filling pressures and reported good correlations.

The change in $e'$ velocity with exercise is another index that has been reported to predict exercise capacity in patients with diastolic dysfunction. In these studies, the change in annular $e'$ velocity with exercise identified the abnormalities in the different patient groups, emphasizing the need to consider diastolic stress testing in patients when there is a discrepancy between the symptomatic status/exercise tolerance and baseline Doppler findings. Recently, LV twist and untwisting were reported to be of value in patients with hypertrophic cardiomyopathy, but additional studies are needed specifically in DHF.

### Diagnostic Implications

Diagnosis of DHF remains dependent on clinical findings of heart failure in the presence of an EF >45% and with evidence of diastolic dysfunction. Noninvasive assessment of LV diastolic function and filling pressures is highly feasible and is recommended using the $E/e'$ ratio from TD signals at the lateral mitral annulus. GSR$_{w}$ is another promising method for this population, particularly in patients with equivocal values of $E/e'$. Currently, the clinical applications of LV untwisting await additional studies but can play an important role in the future. Diastolic stress testing is an emerging approach for the evaluation of patients with dyspnea and normal EF when there is a discrepancy between clinical findings and Doppler velocities at rest. Additional data are needed in both normal and abnormal subjects across different age groups.

### Therapeutic Implications

The use of $\beta$-blockers and rate-slowing calcium channel blockers is advocated in DHF on the premise that they decrease blood pressure and afterload and prolong the diastolic filling period. However, these drugs can have a direct detrimental effect on LV relaxation and negative chronotropic properties. Therefore, the final balance between all these effects determines the clinical response of a given patient. Diuretics are needed in the presence of signs of volume overload, but caution is needed to avoid a precipitous drop in LV stroke volume. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (and potentially statins) that can lead to regression of not only LV mass but also interstitial fibrosis can be beneficial, in part through their favorable effect on LV stiffness. However, they have not reduced mortality in DHF in randomized controlled studies.

The presence of systolic dysfunction suggests that it is possible to target $\beta$-blockers/cardiac glycosides to these patients. Given the heterogeneity of the population, one could reason that detecting systolic dysfunction at rest or identifying patients with reduced contractile reserve by speckle tracking could be of value in this disease, rather than a universal approach of offering the above drugs to all DHF patients, which did not prove useful in randomized clinical trials.

The presence of systolic dyssynchrony (by TD velocity imaging) could help identify patients for consideration of biventricular pacing. The approach is most feasible in patients in whom the LV lateral wall shows the longest delay in contraction. In addition, RV pacing should be minimized, whenever possible, in hypertensive patients to decrease the likelihood of future heart failure via its detrimental effect on LV synchrony. The reduced chronotropic reserve in some patients raises the possibility of using exercise testing to identify these patients and subsequently offer them atrial pacing therapy that can augment their heart rate response to exercise.

Arterial and ventricular stiffness can increase as a result of advanced glycation end products on collagen. Alagebrium chloride breaks glucose crosslinks and can improve LV compliance. In a small open-label study, after 16 weeks of therapy, it led to a decrease in LV mass by MRI and an improvement in LV filling and quality of life in DHF. However, the drug did not affect arterial stiffness by MRI.

LV hypertrophy has an adverse effect on LV diastolic function, and therapy that prevents/suppresses hypertrophy holds potential. These include rho-kinase and mammalian target of rapamycin inhibitors, antioxidants, phosphodiesterase inhibitors such as sildenafil, agents that enhance calcineurin inhibitory proteins, and histone deacetylase blockers.

### Future Goals

There are several causes of DHF besides hypertension, and noninvasive methodologies are of value in focusing and refining our understanding of this complex syndrome, particularly in light of several recent negative trials. The reasons that patients with hypertension develop DHF are not well understood. However, the implications are tremendous for prevention and therapy. A few studies have implicated changes in matrix metalloproteinases, whereas others have suggested the presence of a reduction in LA systolic function. However, very few studies have evaluated LA diastolic function. In that regard, LA systolic deformation (during ventricular systole), coupled with noninvasive estimates of LV filling pressures, can provide a noninvasive assessment of LA stiffness that can help identify patients with a higher likelihood of developing DHF. The role of LV systolic function remains debatable. Speckle tracking appears well suited to tracking changes in deformation measurements and twist (if any) leading to the development of heart failure. Finally, there is a need for adequately powered studies that can address the above hypotheses definitively.

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### Disclosures

None.
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