# Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure

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| **Aims** | To examine myocardial deformation and rotation in patients with heart failure, and elucidate the underlying mechanisms that account for normal ejection fraction (EF) in patients with diastolic heart failure (DHF). |
| **Methods and results** | Fifty consecutive patients presenting with congestive heart failure (age: $58 \pm 16$ years) underwent simultaneous right heart catheterization and transthoracic echocardiography. Left ventricular (LV) volumes, mass, EF, meridional, and circumferential wall stress were measured in addition to haemodynamic measurements. 2-D speckle tracking was applied to measure longitudinal, radial, and circumferential strain and twist. Twist was reduced only in patients with systolic heart failure (SHF: $5 \pm 2°$, DHF: $13 \pm 6°$, control: $14 \pm 5°$, $P < 0.001$). Circumferential strain was not different between DHF ($-15 \pm 5\%$) and control groups ($-20 \pm 3\%$, $P > 0.05$), though it was significantly lower in patients with SHF ($-7 \pm 3\%$, $P < 0.05$). Importantly, longitudinal (DHF:$-12\%$, SHF: $-4\%$, control: $-19\%$, $P < 0.001$) and radial (DHF: $28 \pm 9\%$, SHF: $14 \pm 8\%$, control: $47 \pm 7\%$, $P < 0.001$) strains were significantly lower in both heart failure groups than in controls, and were depressed to a larger extent in SHF patients than in those with DHF (both $P < 0.05$). |
| **Conclusion** | LV longitudinal and radial strains are reduced, but circumferential deformation and twist are normal in DHF patients. On the other hand, in patients with SHF, longitudinal, radial, and circumferential deformation, and twist are all reduced. Multivariable regression analysis suggests that preserved LV twist and circumferential strain may contribute to normal EF in patients with DHF. |
| **Keywords** | Diastole • Heart failure • Echocardiography |

## Introduction

A normal ejection fraction (EF) occurs in >50% of patients presenting with heart failure symptoms.[1] This group has been referred to as heart failure patients with normal EF, or diastolic heart failure (DHF). Their mortality[1] can be similar to those with systolic heart failure (SHF). Although it is still controversial whether left ventricularl (LV) systolic properties are reduced or not, these patients maintain a normal stroke volume and EF at rest. The underlying mechanisms accounting for a normal EF in this group have not been well delineated, but are important given their potential influence on the diagnostic and therapeutic strategies used in this population.

We hypothesized that important differences are present in myocardial function between DHF and SHF patients. These differences in turn can contribute to differences in the 3-D distribution of myocardial deformation and LV twist. Recently, speckle tracking echocardiography was successfully applied to the measurement of myocardial deformation and rotation. Specifically, myocardial

deformation in the longitudinal, radial, and circumferential directions can be quantified,[2–6] and LV twist can be measured.[7,8] Therefore, we undertook this study to examine myocardial deformation and rotation in patients with heart failure, and elucidate the contributing mechanisms for a normal EF in patients with DHF.

# Methods

## Study subjects

The study protocol was approved by PAC institutional review board, and patients provided a written informed consent. Fifty consecutive patients presenting with congestive heart failure (age: $58 \pm 16$ years) were enrolled. All were in sinus rhythm, and had simultaneous right heart catheterization and transthoracic echocardiographic imaging. DHF and SHF were diagnosed as we previously described.[1] Seventeen normal healthy subjects who presented for a routine physical evaluation, and had normal echocardiographic findings were included as a control group. These patients were included in previous studies from our laboratory.

## Echocardiographic studies

All the patients were imaged in a supine position using a GE Vivid 7 ultrasound system. 2-D grayscale images were acquired in the standard parasternal and apical (apical 4, apical 2, and apical long) views at a frame rate of 80–100 frames/s, and three cardiac cycles were recorded. Parasternal short-axis views were acquired at 3 levels: basal, mid-papillary, and apical. In the apical 4-chamber view, mitral inflow and flow propagation velocity (Vp) were recorded as previously described[9] at end expiration. All the images were stored digitally for subsequent offline analysis.

## Echocardiographic analysis

The analysis was performed offline using EchoPac workstation without knowledge of haemodynamic data. Quantification of LV and LA volumes, and LV mass was performed according to the recommendations of the American Society of Echocardiography.[10] Meridional ($ESS_m$) and circumferential ($ESS_c$) LV end-systolic wall stress were calculated.[11] Mitral inflow and Vp were analysed as previously described.[9]

Myocardial deformation measurements were performed using tissue speckle tracking. In each of the apical 4, 2, and long-axis views, a global longitudinal strain curve was obtained, with all LV myocardial segments considered as the region of interest.[6] The average value of peak systolic longitudinal strain from the three apical views was then calculated as global LV longitudinal strain ($GSI_l$). From each of the three short-axis views, a global circumferential strain curve was obtained. The average of peak global circumferential strain from the three short-axis views was calculated as global LV circumferential strain ($GSI_c$). Radial strain ($GSI_r$) was measured in all 16 segments at the three short-axis views and averaged for final analysis.

In addition, cardiac rotation was computed using speckle tracking.[7,8] Counterclockwise rotation was marked as a positive value and clockwise rotation as a negative value when viewed from the apex. The rotation traces of the basal and apical LV cross-sections were exported into MATLAB program (Mathworks, Natick, MA) and the difference between apical and basal rotations at each corresponding time point was calculated as LV twist.

## Haemodynamic measurements

The pressure transducers were balanced prior to data acquisition with the zero level at mid axillary line. Pulmonary artery (PA) catheters were used to measure PA pressures, mean right atrial (RA) pressure and mean wedge (PCWP) pressure. The wedge position was verified by changes in waveform and $O_2$ saturation.

## Statistical analyses

Continuous data are presented as mean $\pm$ SD and dichotomous data in number and percentage. Comparisons were performed with one-way ANOVA if the data were normally distributed; otherwise, one-way ANOVA on ranks if the data distribution was not normal. Pairwise multiple comparison procedures were performed using the Holm-Sidak, or Dunn's method. The relationship between continuous variables was analysed using regression analysis. Selection of independent variables for prediction of LV twist was performed using forward stepwise multivariable analysis. ROC analysis was used to select cutoff values to distinguish DHF patients from SHF and normal controls. A $P$-value $\leq 0.05$ was used to define a significant result.

# Results

The DHF group comprised 20 patients with EF $\geq 50\%$ and elevated PCWP ($>12$ mmHg). The SHF group comprised 30 patients with EF $< 50\%$ and elevated PCWP. All patients had adequate echocardiographic images for interpretation, except for three patients (6%), where cardiac twist could not be reliably measured. Fifty per cent of the patients in the DHF group had stage II diastolic dysfunction, and the other half had restrictive LV filling. Two-thirds of the patients in the SHF group had restrictive LV filling, with the remaining third showing a pseudonormal filling pattern.

## Clinical characteristics

DHF patients were significantly older than those with SHF and controls ($P < 0.001$, *Table 1*), and there were more females in the controls than the two patient groups ($P = 0.008$). On the other hand, body mass index was lower in the control group than in the DHF and SHF groups ($P < 0.001$). Heart rate and mean PCWP were significantly different in DHF and SHF groups in comparison with the control group ($P < 0.001$ for all), but these variables were not different between DHF and SHF groups ($P > 0.05$ for all). Systolic blood pressure (SBP) was higher in DHF group than in SHF group ($P < 0.001$). The prevalence of hypertension, diabetes, and coronary artery disease was not different between DHF and SHF groups ($P > 0.05$).

## Cardiac function

LV end-diastolic volume (EDV), LV end-systolic volume (ESV), LV mass, mESS, cESS were significantly lower in the DHF and control groups in comparison with patients in the SHF group ($P < 0.001$ for all, *Table 2*). However, these variables were not significantly different between DHF patients and the control group ($P > 0.05$ for all). LA volume was larger in both heart failure groups, in comparison with the control group ($P < 0.001$).

LV twist was reduced in patients with SHF in comparison with the control group ($P < 0.05$), but was similar between DHF patients and the control group ($P > 0.05$). Similarly, $GSI_c$ was not different between DHF and control groups ($P > 0.05$), though it was significantly lower in patients with SHF ($P < 0.05$). Importantly, $GSI_l$ and $GSI_r$ were significantly lower in both heart failure groups than in controls ($P < 0.001$), and were depressed to a larger extent in SHF patients than in those with DHF ($P < 0.05$, *Figure 1*). Upon

**Table 1** Clinical characteristics of the study sample

| Variables | DHF (n = 20) | SHF (n = 30) | Control (n = 17) | *P*-value |
|---|---|---|---|---|
| Age, years | 63 ± 16*,** | 52 ± 15* | 42 ± 11 | <0.001 |
| Female gender, *n* | 7* | 6* | 12 | 0.008 |
| BMI, kg/m² | 29 ± 7* | 31 ± 8* | 24 ± 6 | <0.001 |
| CAD | 15 | 20 | 0 (NA) | 0.47 |
| Diabetes mellitus, *n* | 7 | 12 | 0 (NA) | 0.80 |
| Hypertension, *n* | 13 | 8 | 0 (NA) | 0.053 |
| Heart rate, b.p.m. | 86 ± 17* | 86 ± 16* | 65 ± 13 | <0.001 |
| SBP, mmHg | 129 ± 24** | 108 ± 17* | 124 ± 13 | <0.001 |
| DBP, mmHg | 63 ± 16 | 64 ± 15 | 72 ± 12 | 0.05 |
| PCWP, mmHg | 16 (13–22)* | 23 ± 6* | 10 ± 2 | <0.001 |

NA, not applicable in controls; BMI, bodt mass index; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*$P < 0.05$ vs. the control group.
**$P < 0.05$ vs. SHF group.

**Table 2** Echocardiographic measurements

| Variables | DHF | SHF | Control | *P*-value |
|---|---|---|---|---|
| LVEDV, mL | 90 (70–105)* | 202 (161–234)** | 101 ± 33 | <0.001 |
| LVESV, mL | 33 (22–45)* | 140 (120–191)** | 36 ± 14 | <0.001 |
| LVEF, % | 63 ± 6* | 24 ± 9** | 64 ± 6 | <0.001 |
| LV mass, g | 123 (85–174)* | 226 (170–321)** | 107 ± 43 | <0.001 |
| ESS$_m$, g/m² | 110 ± 32* | 175 ± 52** | 135 ± 20 | <0.001 |
| ESS$_c$, g/m² | 110 (86–128)* | 227 (202–384)** | 123 ± 31 | <0.001 |
| LA volume, mL | 64 ± 31*,** | 100 ± 34** | 43 ± 16 | <0.001 |
| DT, ms | 191 ± 55* | 156 ± 47 | 176 ± 16 | 0.015 |
| E/Vp | 2.7 ± 1.1** | 3.4 ± 0.9** | 1.3 ± 0.3 | 0.01 |
| Twist, ° | 13 ± 6* | 5 ± 2** | 14 ± 5 | <0.001 |
| GSI$_l$, % | −12 (−13–8)*,** | −4 (−7–3)** | −19 ± 2 | <0.001 |
| GSI$_c$, % | −15 ± 5* | −7 ± 3** | −20 ± 3 | <0.001 |
| GSI$_r$, % | 28 ± 9*,** | 14 ± 8** | 47 ± 7 | <0.001 |

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.
*$P < 0.05$ vs. SHF group.
**$P < 0.05$ vs. the control group.

consideration of only the 12 normal control subjects who were age and gender matched to the DHF patients, the results and conclusions pertaining to strain and twist were unchanged.

## Differentiation of diastolic heart failure patients from normal controls

We tried to differentiate DHF patients from normal controls by GSI$_l$. Using a cut-off value of GSI$_l$ at −16%, DHF patients could be distinguished from normal controls at a sensitivity of 95% and specificity of 95% with an AUC of 0.98 (*Figure 2*).

## Determinants of left ventricular twist

LV twist was not significantly different between females (7°, 25−75th percentiles: 6−13°), and males (7°, 25−75th percentiles:

5−10°, $P = 0.45$), patients with (8°, 25−75th percentiles: 5−10°), and without diabetes (6°, 25−75th percentiles: 5−12°, $P = 0.76$), and patients with (7°, 25−75th percentiles: 5−13°), and without CAD (6°, 25−75th percentiles: 5−11°, $P = 0.25$). However, twist was significantly higher in patients with hypertension (9°, 25−75th percentiles: 6−14°), than those without (6°, 25−75th percentiles: 5−8°, $P = 0.01$).

On univariable analysis, LV twist was significantly related to LVEDV, ESV, mass, EF, mESS, cESS, LA volume, GSI$_l$, and GSI$_c$, but not age (*Table 3*). On multiple regression analysis, LVEF and GSI$_c$ were the only independent predictors of LV twist ($P < 0.0001$) (*Figure 3*). Conversely, twist and GSI$_c$ were the independent predictors of LVEF on multiple regression analysis ($P < 0.0001$).
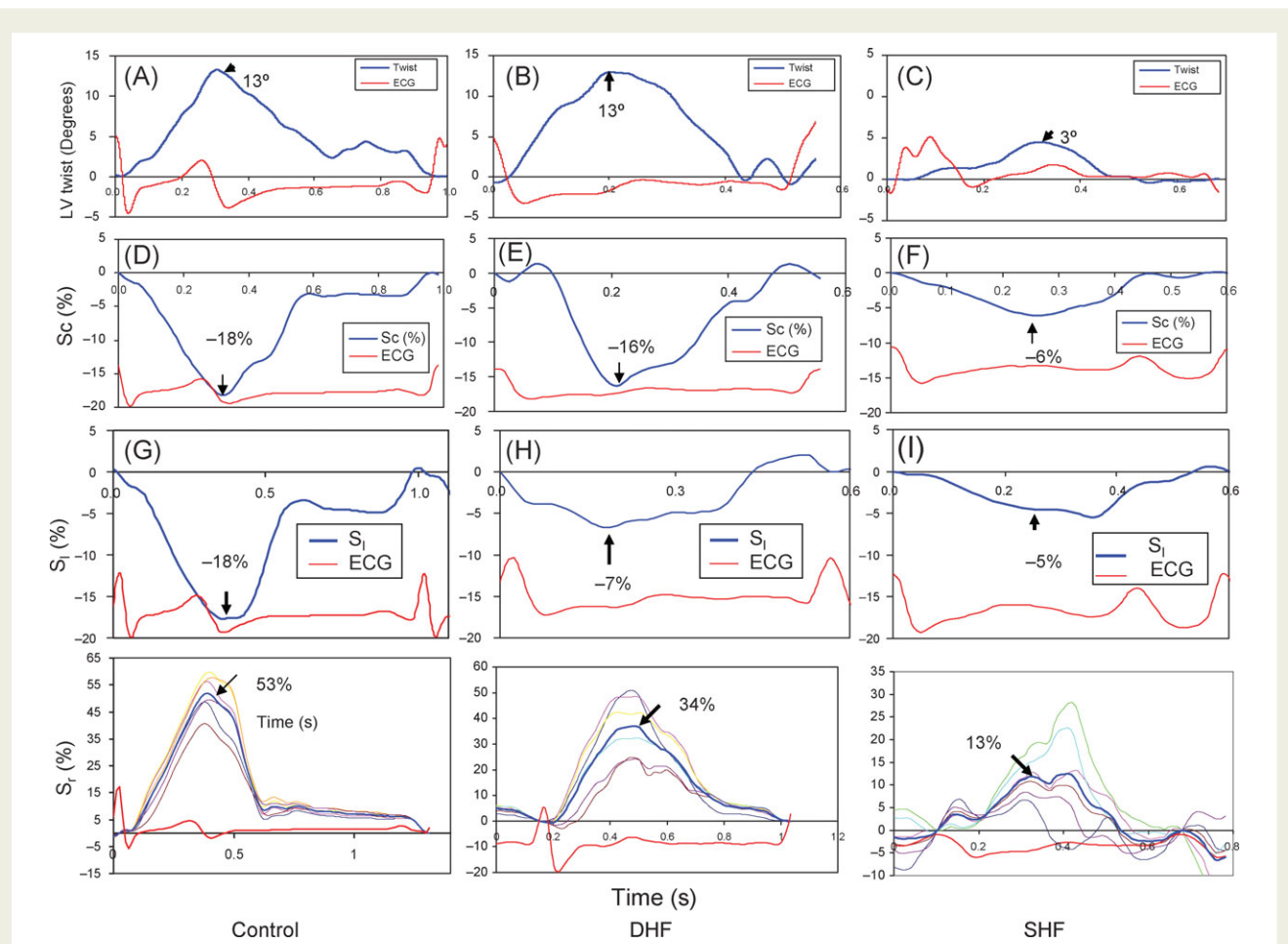
**Figure 1** Examples of twist (upper row), circumferential strain (Sl$_c$: second row), longitudinal strain (Sl$_l$: third row), and radial strain (Sl$_r$: bottom row) from a control subject (left), a patient with diastolic heart failure (DHF: middle), and systolic heart failure (SHF: right). The traces shown for radial strain were obtained from each of the six myocardial segments at the papillary muscle left ventricular short axis level, with the average strain shown in heavy blue and arrows. Notice the presence of normal twist, and circumferential strain in the patient with diastolic heart failure, but lower longitudinal and radial strain in comparison with the control subject
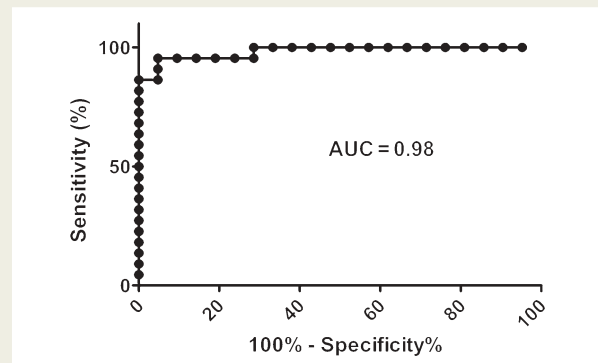


**Figure 2** ROC curve showing the accuracy of global longitudinal strain in differentiating patients with diastolic heart failure from normal subjects. AUC, area under the curve

# Discussion

This study shows that in patients with DHF, LV longitudinal and radial strains are reduced, but circumferential strain and LV twist are preserved. In contrast, longitudinal, circumferential, and radial strain, and LV twist are all impaired in SHF patients. Using LV global longitudinal strain, DHF patients can be accurately distinguished from normal controls.

## Myocardial deformation in diastolic heart failure patients

It is controversial whether systolic function is impaired in DHF patients. Since patients with DHF are not necessarily a homogenous group with respect to their cardiac function, the results have varied with the selected group, as well as the methods used to assess systolic function. Some investigators have not observed abnormal cardiac function in comparison with a

**Table 3** Determinants of left ventricular twist in all patients

| Variables | Mean ± SD | r-value | P-value |
|---|---|---|---|
| Twist, ° | 8.4 ± 5.6 | NA | NA |
| Age, years | 58 ± 16 | 0.20 | 0.13 |
| BMI, kg/m$^2$ | 29.3 ± 7.2 | 0.14 | 0.28 |
| Heart rate, b.p.m. | 84 ± 16 | 0.12 | 0.36 |
| PCWP, mmHg | 18 ± 8 | 0.25 | 0.06 |
| LVEDV, mL | 151 ± 92 | −0.49 | <0.001 |
| LVESV, mL | 95 ± 81 | −0.68 | <0.001 |
| LVEF, % | 44 ± 21 | 0.70 | <0.001* |
| LV mass, g | 198 ± 124 | −0.30 | 0.02 |
| mESS, g/m$^2$ | 139 ± 52 | −0.38 | 0.003 |
| cESS, g/m$^2$ | 178 ± 96 | −0.48 | <0.001 |
| LA volume, mL | 78 ± 36 | −0.30 | 0.02 |
| GSI$_l$, % | −9.0 ± 5.0 | −0.58 | <0.001 |
| GSI$_c$, % | −11.3 ± 6.4 | −0.73 | <0.001* |

BMI, body mass index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.
*Independent predictor of left ventricular twist by multivariable analysis if the variables with significant correlations with left ventricular twist by univariable analysis were included in the model.

control group.[12] Other studies which examined myocardial systolic velocity measurements in the longitudinal plane arrived at opposite conclusions.[13–16] However, mitral annular and myocardial systolic velocities are subject to the effects of tethering and translation. In addition, they are dependent on loading conditions, which must be considered when these measurements are used to draw conclusions on cardiac systolic function. In comparison, myocardial strain measurements have an advantage over velocity indices as they are not affected by tethering and translation. However, they are still affected by loading conditions.[17]

In this study, we measured longitudinal, radial, and circumferential strain by speckle tracking echocardiography and included measurements of preload and afterload to draw conclusions about cardiac systolic function. Important findings include the significantly lower global longitudinal and radial strains in the DHF group in comparison with the control group, but similar circumferential systolic strain (*Table 2*). From the perspective of strain measurements, LV systolic function was clearly better in DHF patients than those with SHF.

Since DHF patients had a similar EDV to that in controls, and a significantly higher wedge pressure, it is reasonable to conclude that preload in the DHF group was not reduced in these patients, in comparison with controls. Therefore, a lower preload does not account for the reduced global longitudinal and radial strains. With respect to afterload, end-systolic meridional wall stress was not different between DHF patients and the control group, and cannot account for the reduced global longitudinal strain.
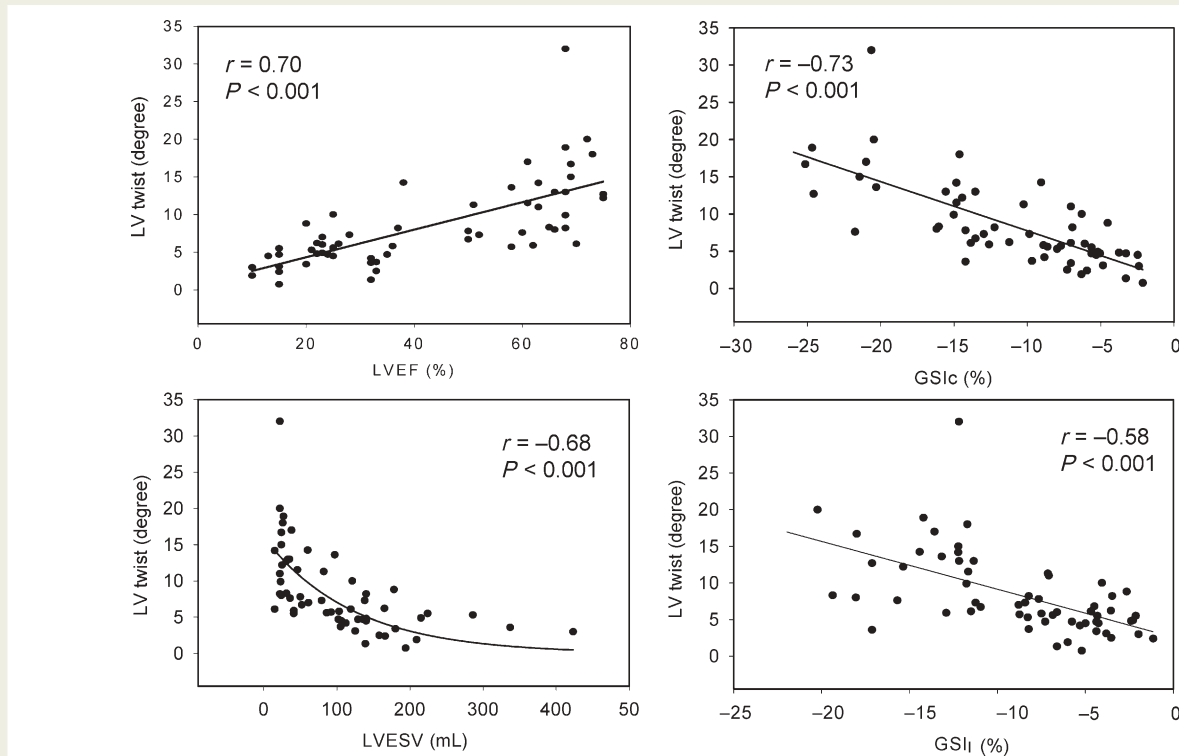


**Figure 3** Regression plot of twist vs. ejection fraction (EF; upper left), circumferential strain (GSI$_c$; upper right), end systolic volume (ESV; lower left), and longitudinal strain (GSI$_l$; lower right)

Accordingly, it is reasonable to infer that a lower intrinsic contractility was present in the DHF patients enrolled in this investigation, and that it contributed to the reduced global longitudinal and radial strains. Interestingly, despite the reduced global LV longitudinal and radial strains, circumferential strain was similar in DHF patients and normal controls.

## Reasons for the difference in longitudinal and circumferential strain in diastolic heart failure

DHF patients are older in age, and usually have hypertension, diabetes, and/or coronary artery disease, which can lead to LV macro and microvascular abnormalities, and interstitial fibrosis. Since the endocardium is most susceptible to the deleterious effects of interstitial fibrosis[18] and hypoperfusion, the abnormal longitudinal function can be detected at an earlier stage by examining subendocardial function, by cardiac MR,[19] or as applied in this study global longitudinal strain measurement. On the other hand, at the same stage of the disease, this pathology may not be present in the mid-myocardial fibre layers, resulting in normal circumferential strain.

## Left ventricular twist

LV twist can be measured using different imaging modalities. First, radioactive markers have been applied to measure twist, but are of limited clinical application due to the need for invasive implantation. In recent years, cardiac magnetic resonance imaging has been shown to measure twist accurately by applying the tagging technique. However, this technique is expensive, time consuming, and has limited temporal resolution. Recently, 2-D speckle tracking was validated for the measurement of cardiac rotation and twist. This approach is a simple way to calculate LV twist with a relatively high reproducibility and temporal resolution. Using speckle tracking, LV twist was calculated in 94% of the patients, which reflects a high degree of feasibility, given the nature of the study, wherein we imaged instrumented supine patients, who were undergoing invasive procedures.

Few studies have examined the haemodynamic determinants of LV twist. Gibbons Kroeker *et al.*[20] studied the effect of manipulations of preload, afterload, heart rate, and LV contractility on apical rotation in a canine model. The authors used apical rotation in lieu of LV twist since the apex rotates to a much larger degree than the base, and is the main contributor of LV twist. In this model, preload was the major determinant of apical rotation. The effects of afterload and LV contractility fell within the range of preload effects. However, in an isolated heart model, Dong *et al.*[21] demonstrated that preload, afterload, and contractility were all predictors of twist on multiple regression analysis. The authors argued that preload and afterload indirectly affected LV twist through their influence on LV stroke volume and EF. In cardiac transplant recipients, Moon *et al.*[22] used radiopaque markers, and noted that an increase in LV inotropic state led to an increase in LV twist.

In our study, EDV, ESV, EF, end-systolic wall stress, both longitudinal, and circumferential strain correlated significantly with LV twist by univariable analysis. On multivariable analysis, only LVEF and circumferential strain were the independent predictors of LV twist. These regression results confirm and extend the previous animal and human observations to patients with heart failure.

## Twist in diastolic heart failure

The subendocardial myocardial fibres are oriented as a right-handed helix, whereas the subepicardial fibres are arranged as a left-handed helix. In general, torque is determined by the helical radius, and the larger radius of the subepicardial fibres, results in these fibres being the dominant force for global LV rotation. Therefore, when viewed from the apex, apical rotation occurs in a counterclockwise direction. The subendocardial torque serves in part to counteract this twist. Accordingly, structural changes influencing either subendocardial and/or subepicardial fibres could lead to the imbalance between the two helical torques, and a change in twist.

As discussed earlier, subendocardial function is likely impaired in DHF patients. Therefore, the subepicardial torque plays the dominant role in determining LV twist. This possibly accounts for our observation of a normal twist in DHF patients. However, as the disease progresses, mid-wall and subepicardial myocardium are affected by pathological changes, and therefore LV twist may be reduced in the later stages. In our study, we showed that LV twist was not significantly different in DHF patients from that in normal controls, but was significantly higher than that in SHF patients. This suggests that the abnormality in myocardial function, and/or pathology may have a transmural extent in SHF patients.

In that regard, normal twist may be a compensatory mechanism in DHF patients that allows them to maintain a normal EF, and untwisting/LV filling given the positive relation between LV twist and untwisting rate.[23]

## Limitations

Our study is limited by the small sample size. This was due to the design aimed at including patients with simultaneous haemodynamic measurements. Patients with DHF were older than the other two groups. However, the age difference between the groups in the present study is relatively small, and would not be expected to influence the results. Furthermore, after the inclusion of only age and gender matched subjects, the results were essentially the same. The significantly lower heart rate in control subjects in comparison to SHF and DHF patients is another limitation. Therefore, these preliminary data should be confirmed in larger data sets of hypertensive and DHF patients with carefully matched control groups. A number of patients with DHF were on medications which can affect cardiac function. However, they would be expected to cause a similar depression in all strain measurements, and not a selective reduction in longitudinal and radial strains.

## Conclusions

LV longitudinal and radial strains are reduced, but circumferential deformation and twist are normal in DHF patients. On the other hand, in patients with SHF, longitudinal, radial, and circumferential deformation, and twist are all reduced. The preserved LV twist and circumferential strain appear to contribute to the normal EF in patients with diastolic heart failure.

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