Detection of Left Ventricular Dysfunction by Global Longitudinal Systolic Strain in Patients with Chronic Aortic Regurgitation

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Background: The purpose of this study was to investigate whether global longitudinal strain measured by two-dimensional speckle tracking echocardiography could detect incipient myocardial dysfunction in patients with chronic aortic regurgitation (AR). Disclosing left ventricular (LV) dysfunction is of decisive importance for optimal timing of surgery but challenging because of the altered loading conditions.

Methods: Forty-seven patients referred for aortic valve replacement because of chronic AR were studied, along with 31 healthy controls. Myocardial deformation as determined by longitudinal, circumferential, and radial strain was calculated using two-dimensional speckle-tracking echocardiography technique, in addition to LV volumes, dimensions, and ejection fraction. Strain values were normalized to end-diastolic volume to correct for the volume dependency of deformation.

Results: Global systolic longitudinal strain was significantly lower in patients with AR before surgery compared with the healthy controls ($-17.5 \pm 3.1\%$ vs $-22.1 \pm 1.8\%$, $P < .01$), while global circumferential strain and LV ejection fraction did not differ ($-21.7 \pm 3.4\%$ vs $-22.6 \pm 2.5\%$, $P = .22$ and $59 \pm 5\%$ vs $59 \pm 6\%$, $P = .59$, respectively). However, differences between patients and controls were evident for both longitudinal and circumferential strain when normalized to end-diastolic volume (-0.09 ± 0.04 vs -0.23 ± 0.08, $P < .01$, and -0.11 ± 0.05 vs -0.24 ± 0.08, $P < .01$, respectively). In contrast to their absolute values, both normalized variables demonstrated improvement in myocardial shortening after valve replacement ($P < .01$).

Conclusions: The study demonstrated reduced global longitudinal strain in patients with chronic AR with preserved LV ejection fractions. Global longitudinal strain might therefore disclose incipient myocardial dysfunction with a consequent potential for improved timing of aortic valve surgery. (J Am Soc Echocardiogr 2011;24:1253-9.)

Keywords: Echocardiography, Aortic regurgitation, Strain, Speckle-tracking imaging, Left ventricular function

Optimal timing of cardiac surgery for chronic aortic regurgitation (AR) has been a challenge for years. The development of systolic dysfunction precedes the onset of symptoms in more than one fourth of patients with this condition.[1,2] Preoperative left ventricular (LV) ejection fraction (LVEF) and cavity dimensions are the most important determinants of survival and LV function after aortic valve replacement (AVR) for chronic AR.[3-8] However, volume-derived measures of LV function have important limitations in assessing myocardial contractile function, whereby a series of compensatory mechanisms, including an increase in LV end-diastolic volume (LV EDV) and hypertrophy, can mask underlying changes in myocardial force development. Therefore, to date, there is no established specific diagnostic method to detect changes in LV systolic function before irreversible dysfunction occurs.

Myocardial strain echocardiography has been introduced as a clinical index of regional[9,10] and global[11,12] LV function. Speckle-tracking echocardiography measures strain by tracing tissue scatter in grayscale images and enables the angle-independent assessment of myocardial deformation indices. As it is noninvasive and reproducible, strain might be well suited for follow-up and to guide the timing of surgical intervention.[13-16]

Therefore, the purpose of this study was to investigate whether global systolic strain measured by two-dimensional speckle-tracking echocardiography could detect early onset of myocardial dysfunction in patients with chronic AR and preserved LVEFs.

METHODS

Study Population

We prospectively included 78 individuals: 47 patients with chronic severe AR and 31 healthy age-matched subjects (15 women; mean age, 48 ± 15 years; $P = .86$). The majority of the patients were referred to the Department of Cardiology between October 2003 and October

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Abbreviations
AR = Aortic regurgitation
AVR = Aortic valve replacement
EDV = End-diastolic volume
LV = Left ventricular
LVEF = Left ventricular ejection fraction

2006 with diagnoses of AR and indications for valve replacement according to the American College of Cardiology and American Heart Association guidelines.[17] None of the patients had atrial fibrillation or other concomitant valve disease. Patients with significant coronary artery disease, defined as ≥50% stenosis in any coronary artery, were excluded. We considered 214 referrals, but because of stringent inclusion criteria, the number of patients included in the study was modest. Therefore, an additional 10 patients were included between January 2009 and November 2009. The entire study was done prospectively. Only patients with LVEFs > 50% were included.

Echocardiography

Recordings were performed with a Vivid 7 scanner (GE Vingmed Ultrasound AS, Horten, Norway). They were obtained in the three standard apical planes (four-chamber, two-chamber, and long-axis) and in the parasternal short-axis plane at the mitral tip by conventional two-dimensional grayscale imaging. The average frame rate was 58 ± 19 frames/sec. The digital loops were stored and subsequently analyzed using EchoPAC software (GE Vingmed Ultrasound AS).

M-mode measurements included LV end-diastolic and end-systolic short-axis diameter. LV EDV and end-systolic volume were analyzed using the biplane Simpson's technique, with subsequent calculation of LVEF. End-diastolic and end-systolic LV lengths were measured from the mitral annulus to the LV apex in an apical four-chamber view. Changes in LV end-diastolic shape were determined by the ratio of end-systolic LV length to end-diastolic LV length and the principal radii of curvatures.[18] The principal radii of curvatures were mathematically defined as $r_1 = L^2/2D$ and $r_2 = D/2$, where r_1 is the radius of the lateral wall long-axis curvature, r_2 is the radius of the circumferential short-axis curvature, L is LV length, and D is LV short-axis diameter (Figure 1).

Myocardial longitudinal, circumferential, and radial strain values were calculated using two-dimensional speckle-tracking echocardiography.[19] Regions of interest were manually outlined by marking the endocardial borders at the mitral annular level and at the apex on each digital loop and were adjusted when the automatic tracking was considered suboptimal by visual or automated assessment. Examples of the technique are shown in Figure 2. Conversion from 18 segments to a 16-segment model was performed by averaging longitudinal strain values in the corresponding apical segments in the apical long-axis and four-chamber views. Similarly, circumferential strain was averaged from six LV short-axis segments at the mitral tip level of the left ventricle. End-systole was defined as aortic valve closure as determined in the apical long-axis view. Analysis of strain in the septum and the lateral wall, separately, was performed in the apical four-chamber view. The longitudinal velocities and displacements by Doppler tissue imaging were calculated at the septal and lateral mitral annulus. Deformation parameters were normalized to LV EDV (strain/LV EDV) to correct for the volume dependency of deformation.[20,21]

Furthermore, patients were evaluated using M-mode echocardiography to assess paradoxical septal motion after cardiac surgery, defined as motion of the interventricular septum toward the right ventricle in systole with normal or delayed systolic thickening.

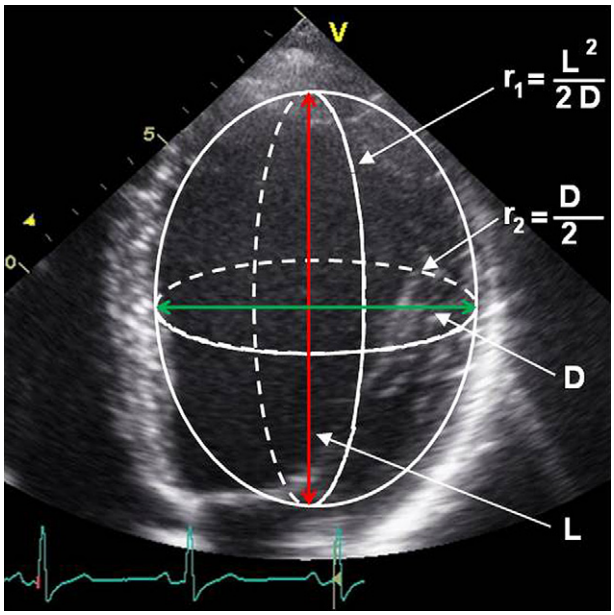

Figure 1 Two-dimensional echocardiogram from a patient with AR before AVR. Changes in LV shape are described by the principal radii of curvature, mathematically defined as $r_1 = L^2/2D$ and $r_2 = D/2$, where r_1 is the radius of the lateral wall long-axis curvature, r_2 is the radius of the circumferential short-axis curvature, L is LV length, and D is LV short-axis diameter.

The echocardiographic studies in patients with AR were performed 58 ± 77 days before and 229 ± 159 days after AVR.

Statistical Analysis

Values are expressed as mean ± SD. Differences between groups were analyzed using independent-samples t tests. Individual differences were tested using paired-samples t tests. Values were compared for correlation by linear regression analysis.

We selected 10 random patients (160 segments) for a reproducibility test of global strain. The reproducibility of LVEF was tested in 20 randomly selected patients. Global strain and LVEF were assessed by two independent observers, and reproducibility was calculated by intraclass correlation (Cronbach's α value). SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL) was used for all statistical analyses. For all statistical comparisons, P values < .05 were considered significant.

The study was approved by the Regional Committee for Medical Research Ethics in Norway, and all subjects gave written informed consent to participate.

RESULTS

In three patients, strain analysis was not feasible, because of poor echocardiographic image quality, and these patients were excluded from further analyses. Clinical characteristics of the remaining 44 patients with AR are shown in Table 1. Approximately one third of the patients had no symptoms at the time of AVR. Because all the patients had normal systolic function as assessed by LVEF > 50%, the indication for surgery in the asymptomatic patients was severe LV dilatation according to the American College of Cardiology and American

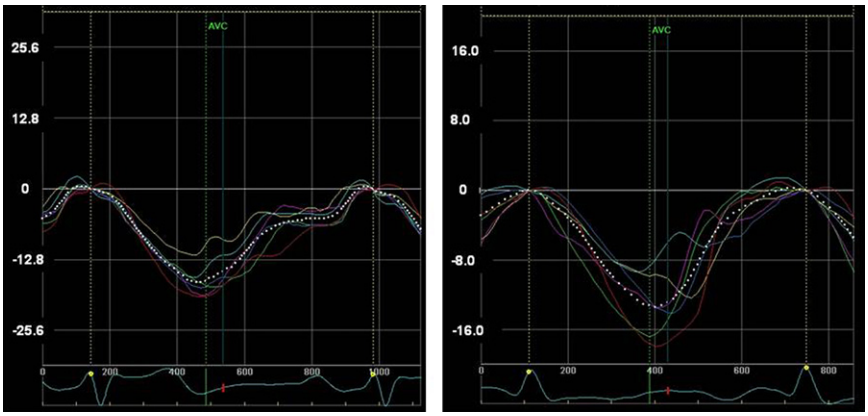

Figure 2 Segmental longitudinal strain measured by two-dimensional speckle-tracking echocardiography from an apical four-chamber view. The curves were obtained from a patient with severe AR before *(left)* and after *(right)* AVR. The global systolic strain is reduced before surgery compared with healthy individuals.

Table 1 Clinical characteristics of patients with AR (n = 44)

Variable	Value
Age (y)	49 ± 14
Men/women	30/14
Medications	
Antiplatelet therapy	6
ACE inhibitors/ARBs	23
β blockers	12
Calcium channel blockers	7
Diuretics	9
Etiology	
Idiopathic dilatation of the aorta	17
Bicuspid valve	14
Previous endocarditis	7
Rheumatic heart disease	1
Aortic valve prolapse	2
Calcific degeneration	2
Unknown	1
NYHA functional class	
I	17
II	17
III	7
IV	3

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *NYHA*, New York Heart Association.
Data are expressed as mean ± SD or as numbers.

Heart Association guidelines.[17] The most common etiologies of AR were dilated ascending aorta, bicuspid aortic valve, and previous endocarditis. Fifteen of the patients with AR (34%) underwent AVR as part of an ascending aortic composite graft.

Before Surgery

Echocardiographic findings are presented in Table 2. Global systolic longitudinal strain was significantly lower in patients with AR before surgery compared with the healthy individuals, while global circumferential strain did not differ. However, differences between patients and controls were evident for both longitudinal and circumferential strain when normalized for EDV. The individual data demonstrated a large overlap between the absolute strain values in patients and controls that was partly overcome when normalized to LV EDV, in particular for global longitudinal strain (Figure 3). LV dimensions and volumes, at both end-diastole and end-systole, were larger in patients with AR, while LVEF did not differ between patients and controls.

After Surgery

Figure 4 demonstrates individual longitudinal strain values before and after surgery.

Longitudinal strain decreased significantly (Table 2, Figure 4) and circumferential strain remained unchanged after surgery (Table 2). Importantly, however, the normalized strain values increased significantly after the operation, although to a level still less than in the control subjects.

Paradoxical septal motion was not observed preoperatively but was found in 24 of the patients (55%) after valve replacement. Longitudinal strain in the lateral wall increased by −0.9%, while septal function decreased by 3.3% (P<.01) after surgery. Longitudinal velocity and displacement decreased in the septum after surgery but increased in the lateral wall (Table 2). This was confirmed by comparing the change in longitudinal strain between the septum and the lateral wall before and after AVR. The differences were −3.6% (P < .01) in patients with paradoxical septal motion and 2.4% (P = .14) in those without.

LV dimensions and volumes were significantly reduced after surgery (Table 2). The decrease was greater for LV EDV than for end-systolic volume, implying reduced LVEF. Only eight patients had increases in LVEF after surgery. Systolic atrial pulmonary pressure was reduced from 27.1 to 23.5 mm Hg (P = .035) after AVR.

Differences in LV Shape

LV shape (Figure 1) was characterized by a more spherical geometry in patients with chronic AR compared with controls. However, there was a decrease in LV end-diastolic short-axis and long-axis dimensions after surgery (66 ± 8 vs 54 ± 6 mm, P<.01, and 96 ± 11 vs 89 ± 10 mm, P<.01, respectively), with the most pronounced decrease of the short-axis dimension. As a result, the end-diastolic short-axis–to–long-axis ratio was reduced from 0.69 ± 0.10 to 0.61 ± 0.10 (P<.01) after surgery, similar to what was observed in controls (0.59 ± 0.05, P = .47). Consistently, the radius of the short-axis curvature decreased after surgery (31 ± 8 vs 25 ± 8 mm, P<.01) while the radius of the long-axis radius curvature increased (71 ± 15 vs 77 ± 18 mm, P<.01).

Table 2 Comparison of echocardiographic findings in patients and controls

Variable	Patients before surgery (n = 44)	P	Patients after surgery (n = 44)	Controls (n = 31)	P^*	$P^\dagger$
Global longitudinal strain (%)	−17.5 ± 3.1	.01	−16.1 ± 3.1	−22.1 ± 1.8	<.01	<.01
Normalized global longitudinal strain	−0.09 ± 0.04	<.01	−0.12 ± 0.04	−0.23 ± 0.08	<.01	<.01
Global circumferential strain (%)	−21.7 ± 3.4	.55	−21.1 ± 4.1	−22.6 ± 2.5	.22	.07
Normalized circumferential strain	−0.11 ± 0.05	<.01	−0.16 ± 0.06	−0.24 ± 0.08	<.01	<.01
Radial strain (%)	51.7 ± 18.5	.81	41.5 ± 16.6	59.4 ± 20.3	.14	<.01
Septal longitudinal velocity (cm/sec)	5.8 ± 1.4	<.01	4.8 ± 1.2	6.6 ± 0.8	.01	<.01
Lateral longitudinal velocity (cm/sec)	6.2 ± 1.6	<.01	7.2 ± 1.8	7.0 ± 1.6	.09	.479
Septal longitudinal displacement (cm)	11.4 ± 3.9	<.01	9.7 ± 3.0	13.7 ± 1.8	.03	<.01
Lateral longitudinal displacement (cm)	10.3 ± 3.3	<.01	12.5 ± 3.7	13.0 ± 2.4	<.01	.46
LVEF (%)	59 ± 5	<.01	54 ± 7	59 ± 6	.59	<.01
LV EDV (mL)	214 ± 71	<.01	141 ± 36	105 ± 30	<.01	<.01
LV ESV (mL)	93 ± 36	<.01	68 ± 24	43 ± 15	<.01	<.01
Left atrial ESV (mL)	71 ± 27	.47	70 ± 29	55 ± 17	.03	.03
SEDD (mm)	66 ± 8	<.01	54 ± 7	50 ± 5	<.01	.04
SESD (mm)	44 ± 8	<.01	36 ± 7	32 ± 4	<.01	.02
End-diastolic LV length (mm)	96 ± 11	<.01	89 ± 10	86 ± 9	<.01	<.01
End-systolic LV length (mm)	78 ± 9	.70	77 ± 10	51 ± 5	<.01	<.01
SV (mL)	163 ± 36	<.01	74 ± 19	62 ± 17	<.01	.01
Systolic blood pressure (mm Hg)	142 ± 25	<.01	131 ± 16	135 ± 21	.26	.42
Diastolic blood pressure (mm Hg)	66 ± 12	<.01	77 ± 12	77 ± 11	<.01	.90
Heart rate (beats/min)	68 ± 12	.24	66 ± 13	71 ± 12	.41	.12

ESV, End-systolic volume; *SEDD*, end-diastolic short-axis diameter; *SESD*, end-systolic short-axis diameter; *SV*, stroke volume.
Data are expressed as mean ± SD.
*Patients before surgery versus controls.
†Patients after surgery versus controls.

Predicting Postoperative LV Function

The correlation between preoperative and postoperative LV EDV was $r = 0.65$ ($P < .01$), while the correlation between preoperative and postoperative normalized global longitudinal strain was $r = 0.62$ ($P < .01$). Global longitudinal strain (without LV EDV correlation) was also correlated regarding preoperative and postoperative values ($r = 0.61$, $P < .01$). Importantly, there was no such correlation for LVEF ($r = 0.17$, $P = .27$), indicating that strain is a superior measurement for predicting postoperative LV function. The correlation between preoperative normalized global longitudinal strain and postoperative LV EDV was $r = 0.58$ ($P < .01$; Figure 5). There was no relationship between changes in LV EDV and longitudinal strain after AVR ($r = 0.11$, $P = .48$) or between left atrial end-systolic volume and preoperative LVEF ($r = 0.09$, $P = .57$) or between left atrial end-systolic volume and postoperative LV EDV ($r = 0.27$, $P = .09$).

Feasibility and Reproducibility

Of all segment analyses, 17% were discarded in the present study. The feasibility of global longitudinal strain was 100% and 84% for circumferential strain. Reliability analysis of strain values revealed Cronbach's α values of 0.98 for intraobserver and 0.95 for interobserver variation. For LVEF, the intraobserver and interobserver variation were 0.84 and 0.81, respectively.

DISCUSSION

The present study demonstrates that global systolic longitudinal strain might be superior to LVEF as a means for detecting subclinical myocardial dysfunction in patients with chronic severe AR. This was indicated by the large proportion of patients with severe AR who had reduced global systolic longitudinal strain preoperatively, despite the presence of normal LVEFs. Optimal timing of surgery is dependent on the identification of reduced myocardial function before it becomes irreversible and negatively affects long-term prognosis. Progressive chamber enlargement will lead to a more spherical geometry and eventually depressed myocardial contractility, supervening adaptive mechanisms to increased load. Unfortunately, such changes may, at least for some time, remain unrecognized by the routinely used imaging modalities.

Current guidelines[17] recommend AVR even without symptoms if the LVEF is reduced to <50%, the end-diastolic diameter increases to >75 mm, or the end-diastolic diameter reaches 55 mm. However, the regular indices of LV function, such as LVEF, may be confounded by changes in preload and afterload. Therefore, volume-derived assessment has important limitations as a measure of LV function in patients with altered loading conditions, which is invariably present in severe AR. In addition, the detection of impaired LV function by LVEF presupposes dysfunction of a certain number of ventricular segments. Thus, LVEF might be insensitive to small decrements in function associated with early changes of myocardial contraction.[11] However, strain would be expected to be a more sensitive measure in this respect, because it directly measures myocardial deformation.

The blood pressure of the patients with AR decreased significantly after AVR, resulting in reduced afterload. This would be expected to translate into increased strain, but our study demonstrated a slight decrease in myocardial shortening after valve replacement. Factors other than afterload might therefore be of importance.

The change in longitudinal shortening associated with AR was more evident than the change in circumferential shortening, because

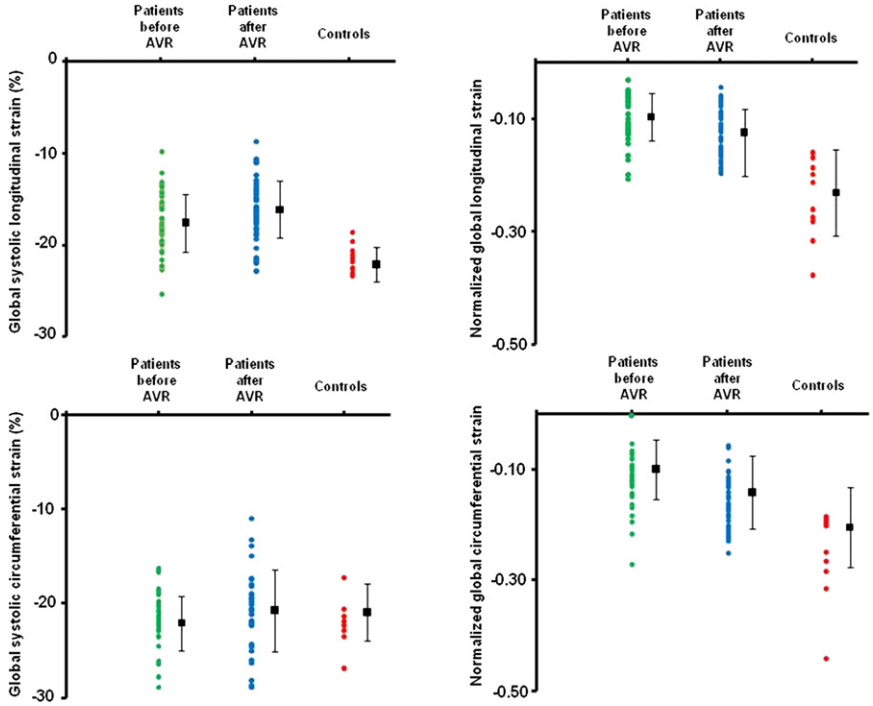

Figure 3 Individual data for global systolic longitudinal and circumferential strain in patients and controls, expressed in absolute values and values normalized to LV EDV.

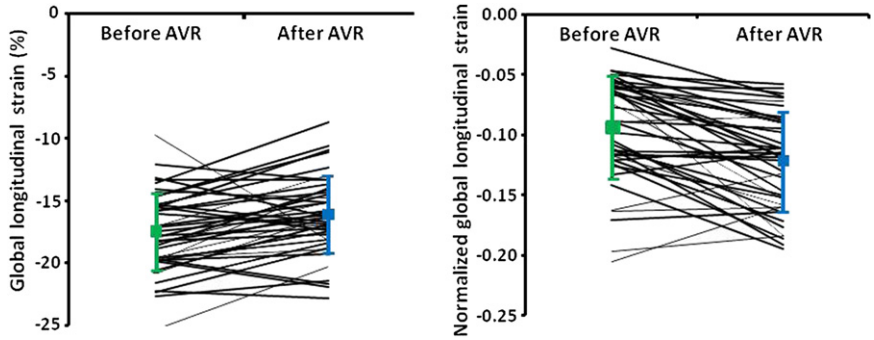

Figure 4 Individual changes in global longitudinal strain and normalized global longitudinal strain after AVR.

global longitudinal strain was found to be reduced even without normalization for preload. The apparently normal global circumferential strain goes along with the normal LVEF, which also predominantly reflects circumferential deformation of the ventricular wall. Thus, the seemingly normal circumferential function might be explained by the compensatory increase in stroke volume consequent to the augmented volume load and increased sphericity of the left ventricle due to AR. Moreover, the enlarged LV cavity is associated with elevated ventricular wall stress, which might imply that the initial and subclinical decrease in LV function starts in the subendocardium, where the longitudinal myocardial fiber orientation dominates. This might add to the strain abnormalities observed in other myocardial diseases involving the development of myocardial fibrosis, such as myocardial infarction[13] and hypertrophic cardiomyopathy.[22] Consequently, assessment of longitudinal LV function by global longitudinal strain seems to be an appropriate and sensitive means for detecting subclinical LV dysfunction in patients with AR. These findings are further supported by measurements of myocardial velocities and displacement. The longitudinal velocity data were lower in patients before surgery compared with normal individuals and normalized in the LV lateral wall after surgery.

As noted, strain normalized for preload appeared to increase the capability to detect incipient LV dysfunction. Thus, there was markedly less overlap between the normalized data in the patient and control group compared to the absolute strain values. Normalized strain seems also otherwise to describe LV function more correctly. Accordingly, the apparent decrease in LV function after surgery as determined by absolute values of longitudinal strain turned out to be erroneous, because the normalized strain demonstrated improved LV function after the operation. These findings on normalized strain are in keeping with a recent report by Marciniak *et al.*[20] They analyzed regional longitudinal deformation parameters from the apical four-chamber view and found that myocardial function progressively decreased with the severity of AR. Importantly, these findings were even more pronounced when the deformation parameters were corrected for geometry. Our study is also in line with a study by Kass and

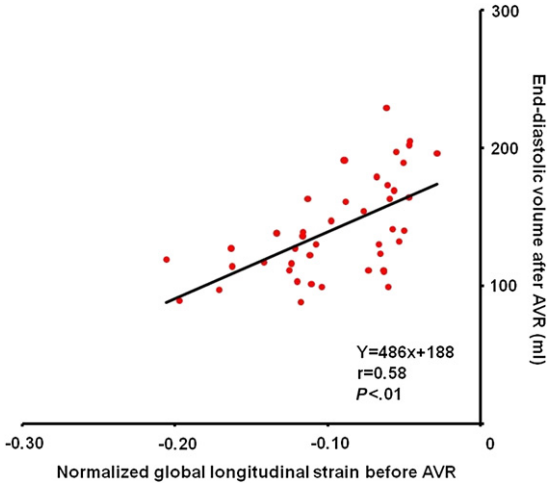

Figure 5 Correlation between preoperative normalized global longitudinal strain and postoperative LV EDV.

Beyar[23] showing that dividing maximal ventricular power by the square of LV EDV gives an index fairly free of load dependence yet sensitive to inotropic state. In our study, the most striking change after AVR was in volume. There was, however, no significant relationship between changes in strain and changes in volume, indicating that the decrease in myocardial shortening cannot be explained by the changes in volumes.

There was a small, but significant, decrease in LVEF after AVR. These results are in accordance with those of Pomerantz *et al.*[24] but differ from the results of others[2,25] who showed an increase in LVEF after AVR. Importantly, we included only patients with normal LVEFs. Increases in LVEF in patients with AR after surgery have been shown only in patients with reduced LVEFs before surgery.[16,26]

In our study, normalized global longitudinal strain demonstrated slightly better LV function after surgery. This was further supported by improved postoperative lateral longitudinal function, while septal longitudinal displacement and velocity were reduced compared to preoperative findings. The latter can partly be explained by findings of paradoxical septal motion. It is well known that paradoxical septal motion is common after coronary artery bypass surgery and has been linked to pericardiotomy and reduced right ventricular function.[27,28] In the patients with paradoxical septal motion, longitudinal strain decreased significantly in the septum after surgery but increased in the lateral wall. Delayed septal contraction, which occurs in those with paradoxical septal motion, will partly facilitate an increase in lateral wall deformation due to the LV pressure alterations.[29]

In the present study, global strain demonstrated better reproducibility than LVEF. Endocardial borders are difficult to outline correctly in patients with poor echocardiographic quality. The region of interest for myocardial strain measurements is placed between the endocardial and epicardial borders of the left ventricle. Consequently, strain measurements are less dependent on excellent endocardial border detection and may therefore be more suitable for the detection of small changes in myocardial function on an individual level compared with LVEF.

Normalized global longitudinal strain was better than LVEF also in predicting postoperative outcomes. By linear regression analyses, there was a significant relationship between preoperative and postoperative values for global systolic strain, but not so for LVEF.

There was a marked decrease in LV EDV after AVR. However, there was no significant relationship between changes in strain and changes in LV EDV. Therefore, the decrease in myocardial shortening cannot be explained by the changes in LV EDV.

Many outcome studies use LVEF as a gold standard. However, our study indicates, in conformity with other studies, that strain is more accurate than LVEF. In the absence of an accepted gold-standard method, no model to predict improvement after AVR is undertaken.

Clinical Perspectives

Both reduced normalized global longitudinal systolic strain and reduced annual velocities might be earlier and more sensitive indicators of myocardial dysfunction and may represent a means for improving decisions regarding the timing of AVR. As demonstrated in our study, speckle-tracking analysis can detect deterioration in LV function before LVEF has declined. The proposed normalized echocardiographic measurements, in addition to annual velocity measurements, can easily be implemented in clinical routine. However, larger studies are required to confirm whether decreases in normalized longitudinal strain and in annual velocities are better indexes of the timing of valve surgery.

Limitations

Because of the strict inclusion criteria, the number of patients was modest. Further studies will be necessary to establish clinical cutoff values for the strain parameters indicating a need for AVR.

Two-dimensional speckle-tracking echocardiographic measurements are, like all echocardiographic techniques, dependent on image quality, and reverberations are a source of error in strain imaging. Assessment of myocardial velocities is angle dependent.

Myocardial damage might occur during the surgical procedure. This might impede the interpretation of our results.

The postoperative echocardiographic examination was performed on average 8 months after AVR. However, there were no incidents in the patients' medical histories indicative of myocardial ischemia between the two examinations.

Global circumferential strain was assessed from only six LV segments, while global longitudinal strain was assessed from 16 LV segments. This adds to the consideration of the longitudinal results being the most important in this study.

CONCLUSIONS

Global systolic longitudinal strain parameters and myocardial longitudinal velocities were reduced in patients with chronic severe AR with normal LVEFs. As opposed to LVEF, global deformation parameters seem capable of disclosing incipient LV dysfunction, especially when normalized for preload. Consequently, normalized global longitudinal systolic strain may be potential means for improved timing of AVR.

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