Comparison of Left Ventricular Systolic Function Quantification Using Contrast-Enhanced and Non-Contrast Echocardiographic Images

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Abstract

Background: Left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) are two important index for the quantification of left ventricular systolic function. With the help of ultrasound contrast agents, we can improve the definition of endocardial borders and allow the quantification of LVEF in patients with poor image quality. However, the feasibility of GLS measurements in contrast-enhanced images is still controversial. Our study aimed to explore the feasibility of GLS measured by velocity vector imaging (VVI) in contrast-enhanced images, compare the difference of measurements in contrast-enhanced and non-contrast images, and analyze the relation between LVEF and GLS in both conditions.

Methods: A total of 133 patients with cancer, who were registered for transthoracic echocardiography as well as contrast-enhanced echocardiography were studied. LVEF was measured using the biplane modified Simpson’s rule and GLS was measured with offline VVI analysis of the three standard apical views in non-contrast and contrast-enhanced images respectively. Linear regression was performed to derive correlation coefficients between LVEF and GLS both in non-contrast and contrast-enhanced images.

Results: GLS measurements in non-contrast images were discarded in 2/133 patients (1.5%), while in contrast-enhanced images were obtained in all patients. LVEF (64.12B7.47% vs. 66.25a8.61%, respectively; $P < 0.01$) and GLS (-20.99c4.67% vs. -23.40k4.58%, respectively; $P < 0.01$) were both significantly higher in the presence of contrast agents. A linear regression between LVEF and GLS in non-contrast images ($r=0.627$, $P<0.001$) was observed, as well as in contrast-enhanced images ($r=0.649$，$P<0.001$).

Conclusion: GLS measured by VVI in contrast-enhanced echocardiography is a feasible and reliable index for the quantification of left ventricular systolic function, even in patients with poor image quality. Compared with the measurements in non-contrast images, both LVEF and GLS measurements are higher in the presence of contrast agents.

1. Introduction

Left ventricular (LV) systolic function is a fundamental part in diagnosis and management of cardiovascular disease, which significantly contribute to hospitalization and mortality. Recommended by American Society of Echocardiography and the European Association of Cardiovascular Imaging, left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) are two main methods for quantification of LV function in echocardiography.[1,2] LVEF, as a conventional parameter, is routinely used in clinical evaluation of LV function to guide the management of different patients, which is proved to be highly correlated with their prognosis.[3,4] However, there are still some limitations with it, including suboptimal endocardial definition caused by poor image quality, geometric assumptions using 2 standard apical views to assess LV function globally and the influence of load-dependent factors.[5]

GLS is also used in the assessment of ventricular function by interpreting myocardial deformation as a percentage change in length. With its additional information over LVEF, GLS shows benefits in various clinical conditions, including evaluation and management of coronary artery disease, cardiomyopathy, valvular heart disease, as well as cardiotoxicity of chemotherapy.[6−8] In addition to that, it has been demonstrated that GLS is an independent predictor of all-cause mortality among patients registered for echocardiography[9 − 11],which can be obtained by two-dimensional speckle-tracking echocardiography (2D-STE). Vector velocity imaging (VVI) is an emerging feature tracking algorithm based on 2D-STE, detecting the myocardial deformation without angular dependence.[12,13] Whereas the poor image quality would also affect the accuracy of GLS measurements because of the suboptimal endocardial border tracking.

Contrast agents, used in left ventricular opacification (LVO), can assist to improve the definition of endocardial borders. Thus, contrast-enhanced echocardiography is recommended to increase the reliability and reproducibility of LVEF measurement.[14,15] However, the feasibility and stability of GLS measurements in the presence of contrast agents are still controversial[16 − 22]. So our purpose of this study were (1) to evaluate the feasibility and stability of GLS measured by VVI analysis in contrast-enhanced echocardiography, (2) to compare the difference of measurements in contrast-enhanced and non-contrast images, and (3) to analyze the relationships between LVEF and GLS in both conditions respectively.

2. Methods

2.1 Study populations

The study was performed on 133 patients with cancer, who registered for both transthoracic echocardiography and contrast-enhanced echocardiography in our laboratory. Medical history and informed consents were obtained from all patients. The exclusion criteria was: (1) atrial fibrillation; (2) patients with histories of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in SonoVue (Lumason, Bracco Imaging, Milan, Italy); (3) patients under 18 years old.

2.2 Echocardiography

All patients were asked to lie in the left lateral position, and 2D gray scale echocardiography was firstly performed using Siemens SC2000 with a 4V1c probe (3.5 MHz), according to American Society of Echocardiography guidelines. Images were acquired when left ventricle was shown clearly on the screen at the frame rate $>$ 40 fps with at least three consecutive cardiac cycles in apical 4 chamber views, apical 2 chamber views and apical 3 chamber views respectively.

Then the contrast agents which we used SonoVue in our study, were prepared with normal saline (NS) in a ratio of 1:5, according to the standard protocol recommended by the manufactures. A trained registered nurse established an intravenous cannula in the patient’s forearm vein opposite to the operator’s positon, and administered 1.5-2 ml of the contrast agents through it with bolus injection in a rate of 1 ml/min for the first 1 ml, and adjusted injection rate for the left ones according to the image quality in time. After that, 5 ml normal saline was administered immediately to wash out the residual contrast agents in the channel. The procedure, which should achieve adequate left ventricular opacification as well as avoid attenuation artifacts, would be repeated if necessary. We use the specific left ventricular opacification settings at the machanical index (MI) of 0.18–0.25 with the focus placed on the level of mitral valves and the tissue equalization (TEQ) set as level 1, adjusting gain and digital gain control (DGC) to optimize images. Images were acquired with at least three consecutive cardiac cycles and at the frame rate $>$ 40 fps, when left ventricle was clearly displayed in all three standard apical views respectively.

2.3 Image analysis

All patients' images were imported into workplace (syngo version 3.0, Siemens Medical Solutions USA Inc., Mountain View, CA) for the offline analysis. Left ventricular volumes and ejection fraction were measured by biplane modified Simpson's rule in both contrast and non-contrast images. GLS was measured by vector velocity imaging (VVI) in the three standard apical views respectively. In this procedure, we chose a frame in systole, which can display the endocardial boarders clearly, and defined the region of interest (ROI) along the borders manually. Whereafter, the software would automatically track position changes of the speckles in the myocardium frame by frame, displaying it by 2D B-mode images multiplied with vector velocity curves. The quality of tracking could be checked on the images, and the ROI could be adjusted again if necessary. When the tracking was confirmed in all three standard apical views, the software would generate the GLS (Fig. 1, D), and show segmental strain (Fig. 1, B, C) with a Bull's-eye result. The analysis was applied in both contrast and non-contrast images, so the GLS in both conditions was obtained respectively.

2.4 Reproducibility

One month after the first analysis, 10 patients' images in both conditions were selected randomly, and analyzed by the same operator blinded to the previous results, assessing the intra-observer variability for GLS. And similarly, the inter-observer variability was assessed by results of 10 randomly selected patients obtained by two different operators who were blinded to the results of each other.

2.5 Statistical analysis

All data were analyzed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). Normally distributed continuous variables were expressed as mean ± SD and compared between two subgroups by t test for independent samples. Paired t test was used in the comparison between measurements in contrast and non-contrast images. Linear regression with Pearson correlation coefficients was used to evaluate the correlation between LVEF and GLS, and the agreement was assessed by Bland-Altman analysis and intraclass correlation coefficient (ICC). All tests were two-tailed and p-value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics

All patients' baseline characteristics are listed in Table 1. We had 133 patients (95 males; age range, 22-84y) with cancer, who registered for contrast-enhanced echocardiography as a baseline examination before chemical therapy in our study. GLS measurements in non-contrast images were discarded in 2/133 patients (1.5%), while in contrast-enhanced images were obtained in all patients. The age, blood pressure and heart rate had no significant difference between different groups.

3.2 Measurements in contrast-enhanced and non-contrast echocardiography

The left ventricular volume, ejection fraction and global longitudinal strain measured in both conditions were listed in Table 2. Both left ventricular volume and ejection fraction are significantly greater in the presence of contrast agents, and the absolute value of GLS is higher in this condition as well.

Patients then were assigned into different subgroups according to their left ventricular systolic function evaluated by EF < 53% as systolic dysfunction in the presence of contrast agents. The variables of patients with normal systolic function and patients with systolic dysfunction is presented in Table 2. The end systolic volume is significantly greater, however the ejection fraction and absolute value of GLS are significantly lower in patients with systolic dysfunction.

3.3 Agreement

The LVEF measured in contrast and non-contrast images are correlated well ($r = 0.712$, ICC = 0.704; $P < 0.01$), and the GLS in different conditions have a good correlation as well ($r = 0.698$, ICC = 0.698; $P < 0.01$) (Table 2). With Bland-Altman analysis, both LVEF and GLS measured in different conditions have a considerable bias and limits of agreement (Fig. 3). In patients with systolic dysfunction (Fig. 4), both EF ($r = 0.829$, ICC = 0.822; $P < 0.01$) and GLS ($r = 0.902$, ICC = 0.897; $P < 0.01$) obtained in the presence of contrast correlated highly with which measured in non-contrast images. However, in patients with normal EF (Fig. 5), the correlation was just moderate for both EF ($r = 0.410$, ICC = 0.408; $P < 0.01$) and GLS ($r = 0.527$, ICC = 0.525; $P < 0.01$.

3.4 Correlation between LVEF and GLS

A linear regression between LVEF and GLS was observed in non-contrast images ($r = 0.627$, $P < 0.001$), which was similar to that observed in contrast-enhanced images ($r = 0.649$, $P < 0.001$) (Fig. 6).

3.4 Reproducibility

The intraobserver variability for GLS without contrast showed a mean difference of -1.60 2.51%, ICC=0.904. Similarly, with contrast, the mean difference was 0.314

2.85%, ICC = 0.846. However, the measurements had significant difference between observers, and the interobserver variability showed a mean difference of 5.61

3.25%, ICC = 0.843 without contrast and 2.51

3.36%, ICC = 0.858 with contrast (Fig. 6).

4. Discussion

Evaluation of LV systolic function is one of the most common indications for echocardiography, which has important implications in diagnosis, management and follow-up of many cardiovascular disease, especially in heart failure. Contrast agents contain some microbubbles and it can increase backscatter of ultrasound by introducing multiple liquid-gas interfaces[23]. So they are now widely applied in clinical to assist the detection of endocardial border thus improve the feasibility and stability of quantification in echocardiography.

4.1 LVEF in different conditions

LVEF as the most widely accepted and routinely used parameter, is currently recommended to be measured using biplane modified Simpson's rule[1], which is the delineation of the LV endocardial borders in two planes. Hence, suboptimal image quality would restrict the tracking of endocardial border and result in a modest accuracy and reproducibility of LVEF.

In our study, we used contrast agents in special LVO settings and found it would improve the image quality and the definition of endocardial border effectively. Compared with non-contrast images, both LV volume and LVEF are significantly higher in the presence of contrast agents. This may be attributed to better visualization of endocardial borders with contrast enhancement and avoiding the foreshortening of LV which could make it hard to define the real apex. A multi-center study by R. Hoffmann et al.[15] compared both contrast and non-contrast enhanced echocardiography with MRI in the assessment of LV volumes and LVEF. They found that both measurements were underestimated in non-contrast images. With contrast enhancement, the agreement between echocardiography and MRI was significantly increased.

4.2 GLS in different conditions

GLS has been shown to be a more sensitive and robust index to detect LV systolic function than LVEF.

And compared with other myocardial deformation parameters like radial and circumferential strains, GLS would be less interfered by potential geometric effect caused by substantial transmural non-uniformity.[24] Hence, it is also recommended as a routine measurement in cancer patients undergoing chemotherapy to detect reduction of LV function prior to the decrease of LVEF[6]. Currently, 2D-STE is widely used to measure GLS, which can track the myocardial speckles without angular dependence. Because GLS is calculated as the average of regional strain, when more than two myocardial segments' tracking is suboptimal, the calculation should be avoided[25]. As we mentioned, contrast agents can improve the image quality in echocardiography, so there is a hypothesis that 2D-STE combined with contrast enhancement may benefit the LV function assessment in these patients with more than two suboptimal segments.

In our study, we found it has a better feasibility to calculate GLS in contrast-enhanced echocardiography using VVI analysis. The absolute value of GLS was significantly higher in the presence of contrast agents, and there was a good correlation between GLS measured with and without contrast agents. In LVO images, we control the speed and dose of the injection of contrast agents to make microbubbles homogenously distributed in LV cavity without far field attenuation or apical swirling. And we use the specific LVO settings with low MI of 0.18–0.25 to reduce the interference of microbubbles perfused in myocardium, so we are able to visualize the real endocardium and make it covered by ROI. While in non-contrast images, only subendocardial and subepicardial region of the walls are used for tracking, then GLS is obtained as the average of them. There are several studies demonstrated that myocardial deformation is characterized by a transmural strain gradient.[26−29] That is potentially caused by the transmural differences in wall stress, which lead to the endocardium stretching longer in diastole and more shortening in systole. Thus, when the tracking of the real endocardium is included, the absolute value of GLS may be higher.

Medvedofsky et al.[16] found that GLS was accurate and reproducible in contrast-enhanced images by using STE software (Epsilon Imaging, Ann Arbor, MI) in patients with poor-quality echocardiographic images. The GLS they measured was just from the analysis of apical four chamber views, however, the anterior wall from apical two chamber views seem to be more vulnerable to poor image quality. Therefore, the assessment of LV systolic function by GLS on the single view may be less accurate. There are also several studies explicated the possibility of speckle-tracking on contrast-enhanced echocardiography with different machine settings and software packages for strain analysis[17 − 22]. Some of them implied that the presence of contrast agents would decrease the feasibility and stability of the tracking[17,19,21,22], so they recommended to perform the analysis after the destruction of microbubbles with high MI. However, the EACVI/ASE inter-vendor comparison study[30] suggested that different vendors and software packages may use different algorithms for optimizing image quality and measuring deformation, which could result in the controversial opinions about GLS measurement on contrast images in these studies as well.

In our study, the strain analysis was performed by VVI software[13,31,32], which is a novel echocardiographic imaging technique based on speckle tracking. It incorporates speckle, mitral annular motion and endocardial border tracking and assesses innermost myocardial function adjacent to the endocardial border. Thus, with contrast enhancement, it may potentially generate more robust results than those algorithms that can only track the speckles in echocardiography.

4.3 Correlation between LVEF and GLS

In non-contrast echocardiography, the correlation between LVEF and GLS is modest, and it is slightly higher with contrast enhancement. That may imply the fact that both LVEF and GLS could be affected by the detection of endocardial border. Onishi et al.[33] found overall linear relationship of GLS and conventional CMR EF, but it appeared to be more curvilinear for subjects with normal EF. Therefore, GLS may have advantage in detection of myocardial dysfunction prior to declination of LVEF, and is recommended in detection of early subclinical cardiomyopathy.

In present study, all patients were divided into two subgroups with EF $< 53\%$ in contrast-enhanced images as systolic dysfunction group, and otherwise as normal group. The agreement of both LVEF and GLS measured in different conditions are better in patients with reduced EF. We found it was easier to control the speed of injection in these patients, because with reduced systolic function, it’s less likely to fill LV cavity with high concentration of contrast agents that may cause far field attenuation and interfere the tracking of basal segments. Another possible reason for that is the etiology of these patients, which cause deposition of fibril proteins in the interstitium of myocardium like cardiac amyloidosis[34]. It's characterized by thickening of ventricular wall and valves and classic granular sparking in myocardium. Hence, the feature tracking of VVI would be performed more accurately in these patients even without contrast.

4.4 Reproducibility

One month after the first analysis, 10 patients were chosen randomly, and their recordings were reanalyzed by the same operator and another operator respectively. We found that the correlation and agreement were good for both non-contrast and contrast-enhanced images for the same operator. However, the interobserver variability level was higher with or without contrast enhancement. That indicates the routine use of VVI requires adequate training for physicians and sonographers to reduce the variability, and for consecutive study, it would be better to perform VVI analysis by the same operator.

Limitations

One limitation of our study is that we didn't include patients with cardiovascular diseases specifically, so there is a small number of patients with reduced LVEF. Meanwhile, we didn't analyze regional strain, thus, we were unable to compare the effect of contrast agents in strain measurements of different segments, or verify the reproducibility of it. However, the purpose of our study is to demonstrate the feasibility of VVI analysis in contrast-enhanced echocardiography and compare the difference of GLS measured with and without contrast enhancement. Global strain can also be computed by averaging the values computed at the segmental level from the same frame, with no more than one segment excluded.[35] So the feasibility of GLS may be better than the strain of one single segment and is more accepted in clinical.

The other limitation is that we didn't assess the LVEF and GLS measurements against CMR as a gold standard. That's because CMR is expensive and time-consuming, and it's hard to be applied in all these patients. At the same time, our focus was on the feasibility and comparison of GLS measured before and after contrast enhancement instead of the accuracy which still need a further study.

5. Conclusion

VVI analysis in contrast-enhanced echocardiography is feasible and reliable, even in patients with poor image quality. Both EF and GLS measurements are significantly higher in the presence of contrast agents, but they have a similar correlation to that in the non-contrast images. So contrast agents may approve us a better way to evaluate the ventricular systolic function. However, more research is still needed to make a standard in the method of GLS measurement with contrast enhancement, including the approach of drug injection and machine settings. And a new reference of GLS at the presence of contrast agents should be established as well.

Declarations

Ethics approval and consent to participate

This study is approved by the local Ethics Committee and the informed consents were obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

SL analyzed and interpreted the patient data and was a major contributor in writing the manuscript. ZW and CY performed the part of patients’ contrast and non-contrast enhanced echocardiography examination. FZ performed a part of patients’ echocardiography and the analyzation of these images. TZ designed the research and was contributor of the manuscript. All authors read and approved the final manuscript

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Abbreviations

ASE American Society of Echocardiography

CMR Cardiac Magnetic Resonance

DGC Digital Gain Control

EACVI European Association of Cardiovascular Imaging

GLS Global Longitudinal Strain

ICC Intraclass Correlation Coefficient

LV Left Ventricle

LVEF Left Ventricular Ejection Fraction

LVO Left Ventricular Opacification

MI Machanical Index

MRI Magnetic Resonance Imaging

ROI Region of Interest

TEQ Tissue Equalization

2D-STE Two-dimensional Speckle-tracking Echocardiography

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Tables

Variable	Value
Age (years)	55.113.41
Male	95 (71.4)
Etiology	
Multiple myeloma (MM)	47 (35.9)
Lymphoma	49 (37.4)
Others	35 (26.7)
SBP (mmHg)	129.7818.26
DBP (mmHg)	78.13±7.56
HR (/min)	79.88±8.56
LVEF (%)	
Non-contrast	64.12±7.47
Contrast-enhanced	66.25±8.61
GLS (%)	
Non-contrast	-20.99±4.67
Contrast-enhanced	-23.40±4.58

Table 1. Population characteristics at inclusion

	All patients	Group 1	Group 2
Non-contrast			
LVEDV (ml)	77.0122.18	72.1926.67	77.1121.56
LVESV (ml)	27.429.59	39.5314.58	26.648.66
LVEF (%)	64.127.47	457.10	65.525.43
GLS (%)	-20.994.67	-11.444.75	-21.623.93
Contrast			
LVEDV (ml)	96.3127.17	90.0424.90	96.09±27.11
LVESV (ml)	32.5212.13	52.0115.84	31.0910.75
LVEF (%)	66.258.61	42.288.06	67.915.93
GLS (%)	-23.404.58	-12.284.2	-24.053.
ICC			
LVEF	0.704	0.822	0.408
GLS	0.698	0.897	0.525

Table 2. Measurements in contrast and non-contrast images (Mean±SD).

LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; ICC: intraclass correlation coefficient

	Non-contrast	Contrast-enhanced
Intraobserver		
CV%	-1.602.51	0.3142.85
ICC	0.904	0.846
Interobserver		
CV%	5.613.25*	2.513.36*
ICC	0.843	0.858

Table 3. Reproducibility

CV: coefficient of variation

ICC: intraclass correlation coefficient

*There has significant difference between the two measurements, P<0.05

Figures

Figure 1

VVI analysis in non-contrast apical four chamber view, and strain analysis. A. The tracking of myocardium by VVI software, and the vector velocity curve is overlapped on 2D gray scale echocardiography; B. segmental strain curves in 3 consecutive cardiac cycles; C. Longitudinal strain and other myocardial deformation parameters; D. Segmental strain values in all three apical views displayed in bullseye plot, longitudinal strain in three views, and global longitudinal strain (GLS).

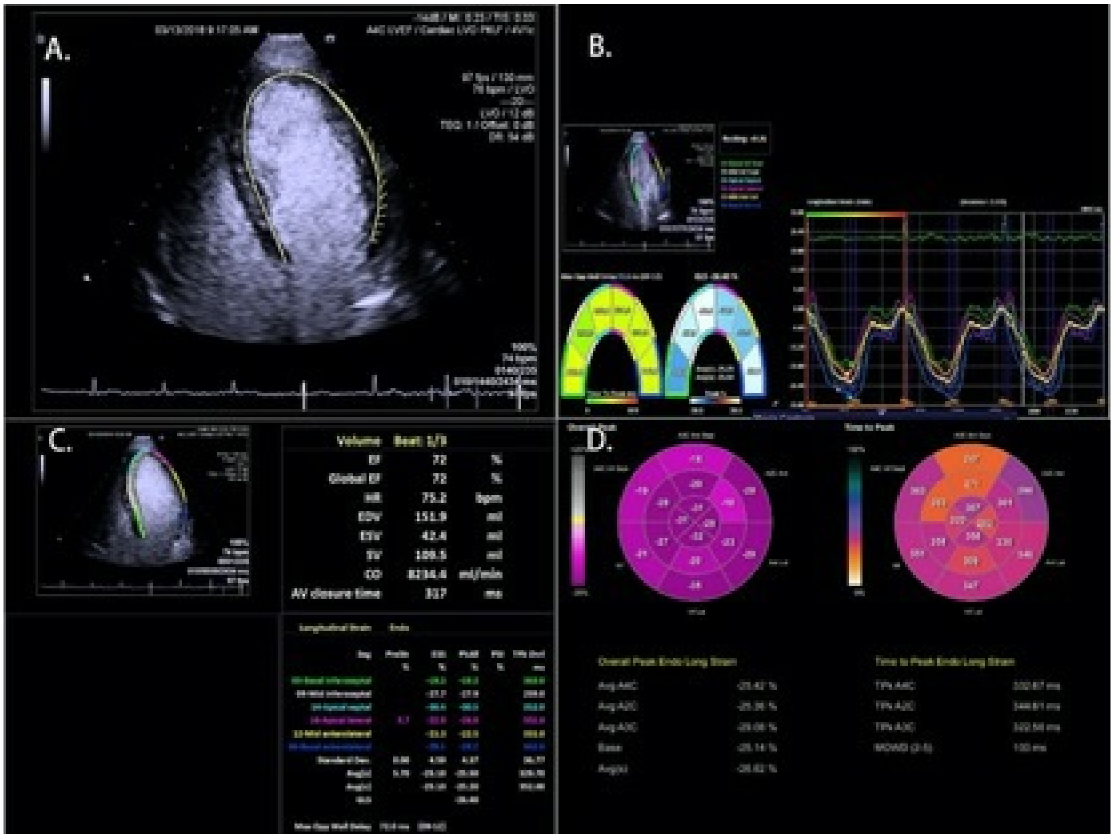

Figure 2

VVI analysis in contrast-enhanced apical four chamber view, and strain analysis. A. The tracking of myocardium by VVI software, and the vector velocity curve is overlapped on 2D gray scale echocardiography; B. segmental strain curves in 3 consecutive cardiac cycles; C. Longitudinal strain and other myocardial deformation parameters; D. Segmental strain values in all three apical views displayed in bullseye plot, longitudinal strain in three views, and global longitudinal strain (GLS).

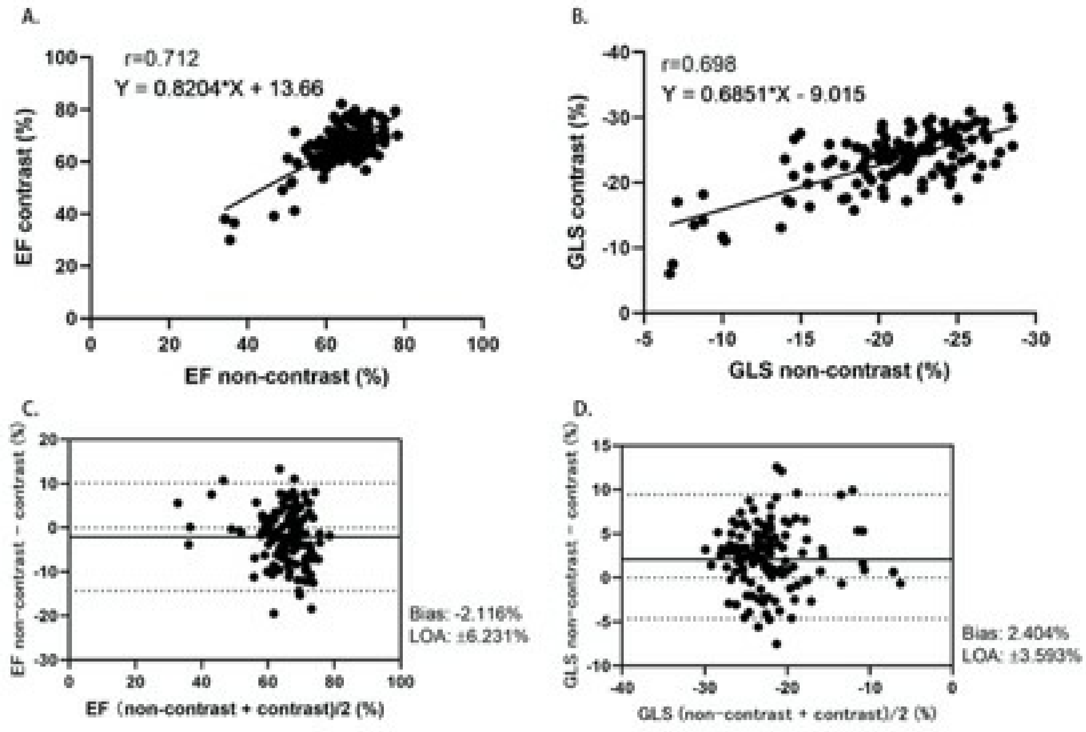

Figure 3

Correlation and agreement between measurements in contrast and non-contrast images. A. The correlation of EF measured in contrast and non-contrast images; B. Agreement of EF by Bland-Altman plot; C. The correlation of GLS measured in contrast and non-contrast images; D. Agreement of GLS by Bland-Altman plot.

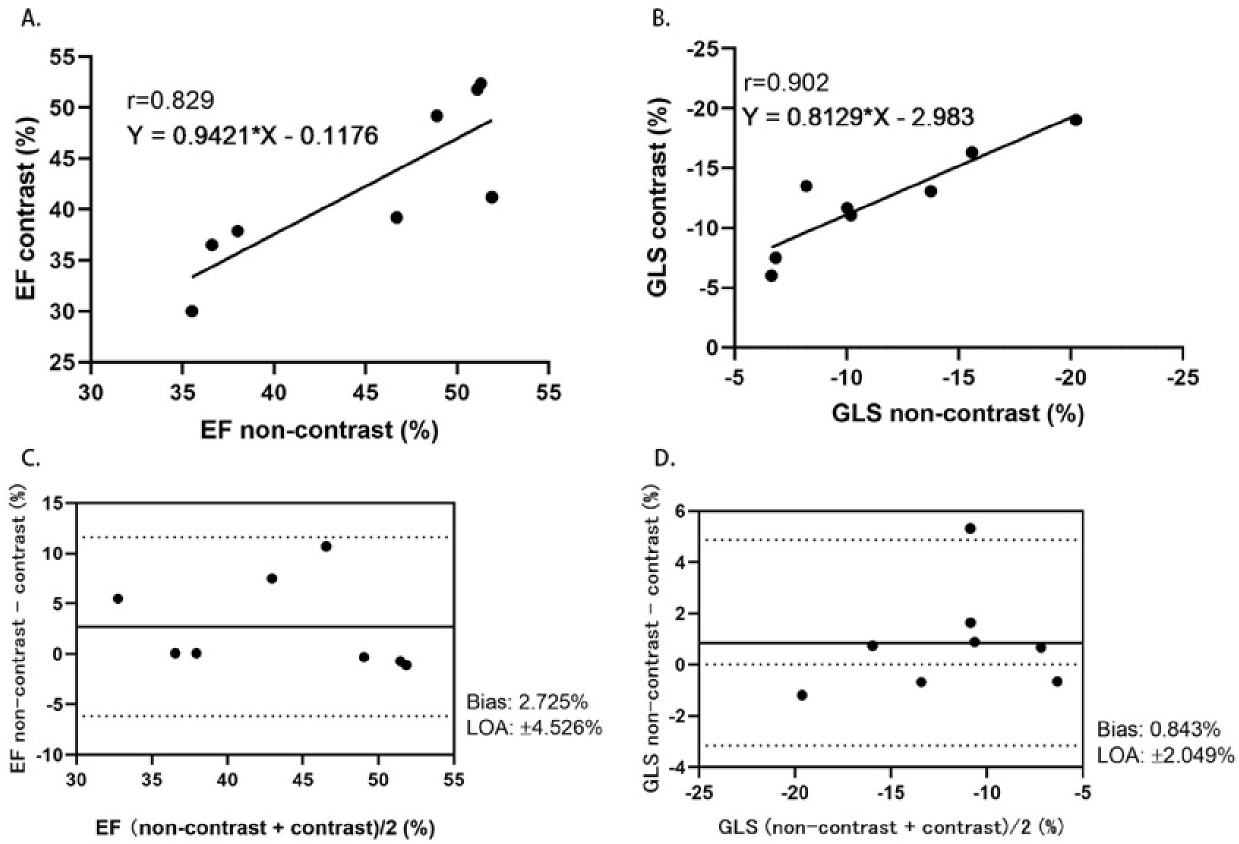

Figure 4

. In patients with reduced EF, measurements have a good correlation and agreement in contrast and non-contrast images. A. The correlation of EF measured in contrast and non-contrast images; B. Agreement of EF by Bland-Altman plot; C. The correlation of GLS measured in contrast and non-contrast images; D. Agreement of GLS by Bland-Altman plot.

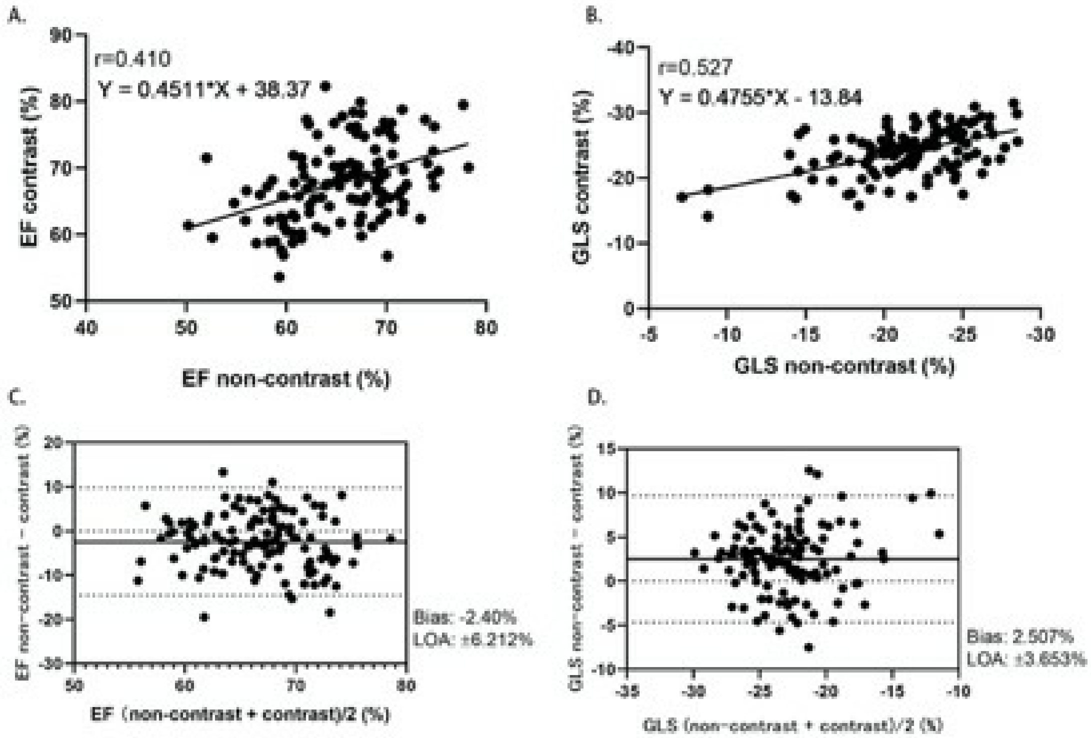

Figure 5

In patients with normal EF, measurements have a modest correlation and agreement in contrast and non-contrast images. A. The correlation of EF measured in contrast and non-contrast images; B. Agreement of EF by Bland-Altman plot; C. The correlation of GLS measured in contrast and non-contrast images; D. Agreement of GLS by Bland-Altman plot.

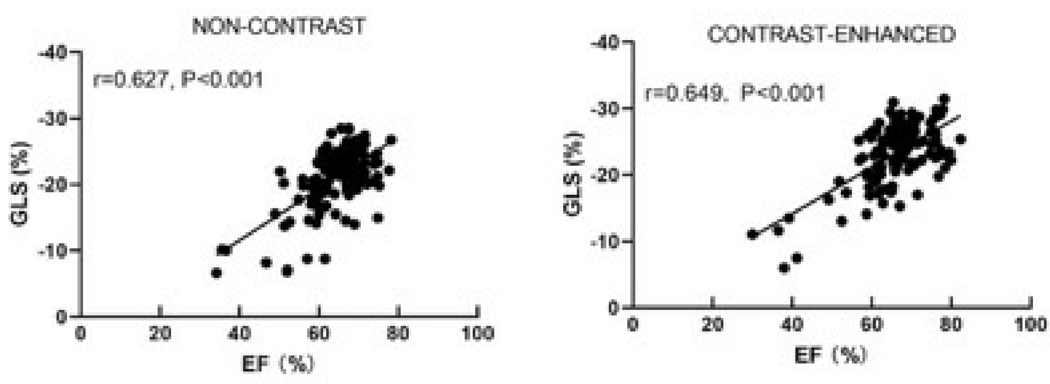

Figure 6

The correlation between EF and GLS in contrast and non-contrast images.