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Title:

Speckle-tracking echocardiography with novel high frame-rate imaging.

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Abstract

Background: global longitudinal strain (GLS) measures myocardial deformation and is a sensitive modality for detecting subclinical myocardial dysfunction and predicting cardiac outcomes. The accuracy of speckle-tracking echocardiography (STE) is dependent on temporal resolution. A novel software enables relatively high frame rate (Hi-FR) (~200 fps) echocardiographic images acquisition which empowers us to investigate the impact of Hi-FR imaging on GLS analysis. The goal of this pilot study was to demonstrate the feasibility of Hi-FR for STE.

Methods: In this prospective study, we acquired echocardiographic images using clinical scanners on patients with normal left ventricular systolic function using Hi-FR and conventional frame rate (Reg-FR) (~50 FPS). GLS values were evaluated on apical 4-, 2- and 3-chamber images acquired in both Hi-FR and Reg-FR. Inter-observer and intra-observer variabilities were assessed in Hi-FR and Reg-FR.

Results: There were 143 resting echocardiograms with normal LVEF included in this study. The frame rate of Hi-FR was 190 ± 25 and Reg-FR was 50 ± 3, and the heart rate was 71 ± 13. Strain values measured in Hi-FR were significantly higher than those measured in Reg-FR (all $p < 0.001$). Inter-observer and intra-observer correlations were strong in both Hi-FR and Reg-FR.

Conclusions: We demonstrated that strain values were significantly higher using Hi-FR when compared with Reg-FR in patients with normal LVEF. It is plausible that higher temporal resolution enabled the measurement of myocardial strain at desired time point. The result of this study may inform clinical adoption of the novel technology. Further investigations are necessary to evaluate the value of Hi-FR to assess myocardial strain in stress echocardiography in the setting of tachycardia.

Keywords

Echocardiography, Speckle-tracking, Frame rate, Global longitudinal strain, Left ventricle.

Abbreviations

2D = 2-dimensional

CAD = coronary artery disease

CI = confidence interval

GLS = global longitudinal strain

Hi-FR = relatively high frame rate

LV = left ventricle

LVEF = left ventricular ejection fraction

Reg-FR = regular (conventional) frame rate

STE = speckle-tracking echocardiography

INTRODUCTION

Echocardiography is the primary imaging modality in evaluating heart disease given its feasibility, easy accessibility, low cost, and lack of ionizing radiation [1]. Global Longitudinal strain (GLS) derived from speckle-tracking echocardiography (STE) detects subclinical myocardial dysfunction and can predict cardiac outcomes [2].

In STE, the pattern of ultrasound signal is tracked frame-by-frame to assess myocardial deformation during a cardiac cycle. The frame rate of conventional 2D echocardiography is approximately 40 – 80 fps which is usually considered adequate to evaluate myocardial deformation at normal heart rates [2–4]. As the accuracy of STE is highly dependent on temporal resolution, a higher frame rate than the conventional 40 – 80 fps may be required to obtain reliable strain values. Several techniques have been proposed in the past few years to increase frame rate in echocardiography while maintaining high image quality [5–7]. In a canine model, validating against myocardial strain directly measured by sonomicrometry, STE with frame rate of 211 fps reliably depicted decreased myocardial function caused by ischemia [8]. Joos P, et al. [7] demonstrated feasibility of myocardial STE at high frame-rate (500 fps) in healthy volunteers using a research scanner. Recently a novel software became available to acquire echocardiographic images at a relatively high frame rate (~200 fps) (Hi-FR) using clinical ultrasound machines. In this prospective pilot study, STE was evaluated using both a standard frame rate (Reg-FR) and Hi-FR (~200 fps) on patients clinically referred for echocardiography examinations. The objective of this study was to compare the values of GLS derived from STE with Hi-FR vs. Reg-FR in a clinical setting.

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METHODS

STUDY DESIGN AND POPULATIONS. This was a prospective study of patients clinically referred to Adult Echocardiography Laboratory at Montefiore Medical Center between April 2017 and July 2018. Consecutive patients who agreed to undergo resting echocardiography with additional image acquisition for the purposes of the study were enrolled. The inclusion criteria was age ≥ 18 years while the exclusion criteria were significant arrhythmias, and suboptimal imaging quality (defined as 2 or more suboptimal myocardial segments for strain analysis [9]). Patients who demonstrated left ventricular ejection fraction < 50% were excluded from this study. The study was approved by the Office of Human Research Affairs at Albert Einstein College of Medicine and carried out according to the principles of the Declaration of Helsinki. This study contained no more than minimal risk to patients, therefore informed consent was waived by the institutional review board.

IMAGING ACQUISITION. The 2-dimensional (2D) echocardiographic images were acquired using commercially available clinical system (EPIQ 7, Philips Healthcare, Andover, MA). All the images were acquired by experienced sonographers, YX and WH. Images were optimized to improve signal-to-noise ratio and provide optimal endocardial definition. Images were acquired to ensure visualization of the largest cavity lengths, and with a less than 20% difference between apical 4- and 2- chamber views. Following the standard clinical protocol, additional apical 4-, 2- and 3-chamber views were acquired with Hi-FR (~200 fps) using Hyper 2D (Philips Healthcare, Andover, MA) software on the same ultrasound machine that was used to acquire clinical images. All the images were stored on digital media (IntelliSpace, Philips Healthcare, Andover, MA) which is the standard protocol at Montefiore Medical Center.

SPECKLE-TRACKING ECHOCARDIOGRAPHY - STRAIN ANALYSIS. Strain analysis was performed using Q-lab strain analysis software (CMQ, Philips Healthcare, Andover, MA), a commercially available software validated for this purpose. GLS values were evaluated on apical 4-, 2- and 3-chamber images acquired in both Hi-FR and Reg-FR (Figure 1). The observer manually traced the endocardial border at end-diastole, and the software automatically tracked the border during a cardiac cycle. Adequate tracking was then visually verified, and the endocardial border was manually corrected if deemed necessary to ensure optimal tracking. After the completion of this tracking process, strain value at each frame was automatically plotted to derive a strain curve. GLS was defined as the strain at end-systole (i.e. at the time of aortic valve closure) from the three apical views (i.e. apical 4-, 2- and 3-chamber views) [2]. LV GLS curve was automatically calculated as the time-to-time average of all three apical views, and LV GLS value was derived at the end-systole.

STATISTICAL ANALYSIS. Data was analyzed using SAS version 9.4 (Cary, North Carolina). All statistical tests were 2-tailed, and a p-value < 0.05 was considered statistically significant. Normality of the continuous variables were checked. Continuous variables were summarized as mean ± standard deviation based on central limit theorem. Categorical variables were presented as counts (percentages). Differences of GLS between Hi-FR and Reg-FR were calculated in apical 4-, 2-, 3-chamber images and the LV using Paired Student T-test, and the

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mean differences [95% confidence interval (CI)] were shown in a forest plot. Inter-observer and intra-observer variability was evaluated in 10 random rest echocardiography studies on both Hi-FR and Reg-FR sets of images [10]. For inter-observer variability, reproducibility was assessed using Pearson correlation coefficients. In addition, reliability was assessed by a percent change between the two observers (e.g. the absolute difference of GLS between Hi-FR and Reg-FR was divided by the mean of the repeated observations). For intra-observer variability, reproducibility was assessed using Pearson correlation coefficients and repeatability was assessed by repeatability coefficient. For assessment of reliability and reproducibility, normality of the continuous variables were checked. Continuous variables were summarized as mean ± standard deviation or median [interquartile range] depending on data distribution.

RESULTS

PATIENT POPULATION and CHARACTERISTICS. A total of 187 patients were recruited for this study, and 44 patients were excluded (27 for suboptimal imaging quality and 2 for severe arrhythmia (e.g. frequent premature ventricular contractions), 15 for low LVEF. The final study population comprised of 143 patients. Characteristics of the cohort are summarized in Table 1.

GLS IN HI-FR VS. REG-FR. The frame rate of Hi-FR was 190 ± 25 and Reg-FR was 50 ± 3, and the heart rate was 71 ± 13. GLS values were compared between Hi-FR and Reg-FR in apical 4-, 2-, 3-chamber views and the LV. Absolute GLS values measured in Hi-FR were significantly larger compared to those measured in Reg-FR (all $p<0.001$) (Figure 2).

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INTEROBSERVER AND INTRAOBSERVER VARIABILITIES. Pearson correlation coefficients between the two observers showed great reproducibility Inter-observer variability in both Hi-FR (r=0.94, p<0.0001) (Figure 3A) and Reg-FR (r=0.94, p<0.0001) (Figure 3B). The reliability calculated as a percent change in two observers was 6.7 [4.4, 7.4] % (p <0.0001) in Hi-FR and 5.5 [4.0, 7.8] % (p <0.0001) in Reg-FR. Intra-observer variability was also evaluated using linear regression model in Hi-FR (r=0.98, p<0.0001) (Figure 4A) and Reg-FR (r=0.95, p<0.0001) (Figure 4B). Repeatability coefficient of Hi-FR was 1.7 % and Reg-FR was 2.4 %.

DISCUSSION

STE has been increasingly adopted for the assessment of LV function in various clinical settings. STE is highly dependent on temporal resolution, and our result indicated that Hi-FR (~ 200 fps) provided higher values than Reg-HR STE (~50 fps). Optimizing GLS measurements is clinically important because GLS is proven to be useful in detecting subclinical LV mechanical changes. The ability of Hi-FR STE to detect true GLS in patients with normal LVEF is potentially powerful and meaningful in clinical setting.

Using a novel software on a standard clinical ultrasound machine, 2D echocardiography images can be obtained with Hi-FR (~200fps) which is more than twice that of the conventional frame rate. The importance of optimizing frame rate has been widely recognized, and it was discussed in expert consensus documents for STE analysis [4,9]. Temporal resolution of echocardiography is regulated by the size of the field of view. In adult echocardiography, certain depth and sector widths are required to visualize the heart, therefore the maximum temporal resolution is finite. Due to this limitation intrinsic to ultrasound physics, STE is currently evaluated at 40-80 fps. Frame rate cannot be modified during post-processing to analyze STE. Historically, tissue Doppler echocardiography was used evaluate ventricular function by strain analysis to circumvent limited temporal resolution [11]. However, Doppler technique is angle dependent. Therefore, strain analysis by 2D STE using ultra-fast frame rate echocardiography has been studied for over a decade [12]. Lee et al. demonstrated the feasibility of STE in canine model to detect ischemic myocardium using STE with similar frame rate to this study by comparing strain evaluated with STE to sonomicrometry [8]. Sonomicrometry is an in-vivo method that directly measures myocardial strain using a paired crystals implanted in the myocardium.

Our results showed significantly higher GLS with Hi-FR compared to Reg-FR in patients with normal LVEF, suggesting Hi-FR is likely more accurate for STE evaluation compared to Reg-FR. The explanation of this finding is illustrated in Figure 5A, showing how a higher frame rate (and hence higher temporal resolution) can allow for a more reliable measurement of true peak strain. Using cine imaging with conventional frame rate, reproducibility of strain values has been verified to be sufficient for clinical use. However, it is important to recognize that reproducibility is to show precision but not necessarily accuracy of the measurements. Therefore, considering the strain wave form in Figure 5, strain values evaluated in Hi-FR are closer to the true GLS (e.g. GLS at the ideal point of end-systole) compared to the values evaluated in Reg-FR.

Furthermore, Hi-FR echocardiography may expand STE application to higher frame rate condition such as stress echocardiography. As stated above, it is generally considered that frame of 40 to 80 fps is relatively low and only adequate for resting heart rate. In case of increased heart rate, there is a potential of underestimating the peak strain value [13]. Previous data on normal myocardial strain response to exercise are somewhat contradictory and limited. In stress echocardiography, the accuracy of detecting significant coronary artery disease (CAD) was reported as 60% using STE with 60 - 100 fps [14]. Joyce, et al. [14] also showed that the GLS at peak stress was smaller than GLS at rest in all their cohort regardless of the presence of significant CAD. Yu Y, et al. [15] also showed a marked decline in strain in individuals without obstructive CAD with dobutamine stress test especially at low doses (-17.6% to -10.8%). Hi-FR has the potential to solve these problems, therefore extending the utility of STE to stress echocardiography in the future.

Our study showed great inter-observer and intra-observer reproducibility of GLS in both Hi-FR and Reg FR by Pearson correlation and linear regression assessment. The inter-observer reliability test showed significant difference between the two observers, however the actual number of percent change between the two observers was less than 8 % that was thought to be reliable. Repeatability coefficient of two measurements by one observer was reasonable in both Hi-FR and Reg-FR. We used a strain analysis software from a single vendor (CMQ, Philips Healthcare) for all the STE analysis, and our observations were consistent with the results reported by EACVI/ASE/Industry Task Force to Standardize Deformation Imaging [16]. Therefore, the STE analysis of this study were precise and reliable.

STUDY LIMITATIONS. This study has some limitations. First, there was a possibility of selection bias because patients with severe arrhythmia or suboptimal image quality were excluded from this study. During severe arrhythmia, it is difficult to assess cardiac function by any methods due to significant beat-to-beat variability. Furthermore, evaluation using suboptimal image quality would result in unreliable results. Therefore, exclusion due to severe arrhythmia or suboptimal image quality are common limitations of cardiovascular imaging studies in general. Secondly, this pilot study only included patient with normal LVEF. Additionally, STE was evaluated only at rest. Future studies are needed to evaluate the utility of Hi-FR in patients with reduced LVEF and also in conditions with increased heart rates. Thirdly, echocardiography images were acquired using echocardiography machines of a single vendor. STE was analyzed using a software of a single vendor as well. Similar studies need to be performed using echocardiography machines and STE analyzing software of different vendors to verify that our results are neutral to vendors.

CONCLUSIONS

We demonstrated that strain values were significantly higher using Hi-FR when compared with Reg-FR in patients with normal LVEF. It is plausible that higher temporal resolution enabled the measurement of strain at the optimal timing. The result of this study may inform clinical adoption of the novel technology. Further investigations are necessary to evaluate the value of Hi-FR to assess myocardial strain in the setting of increased heart rate.

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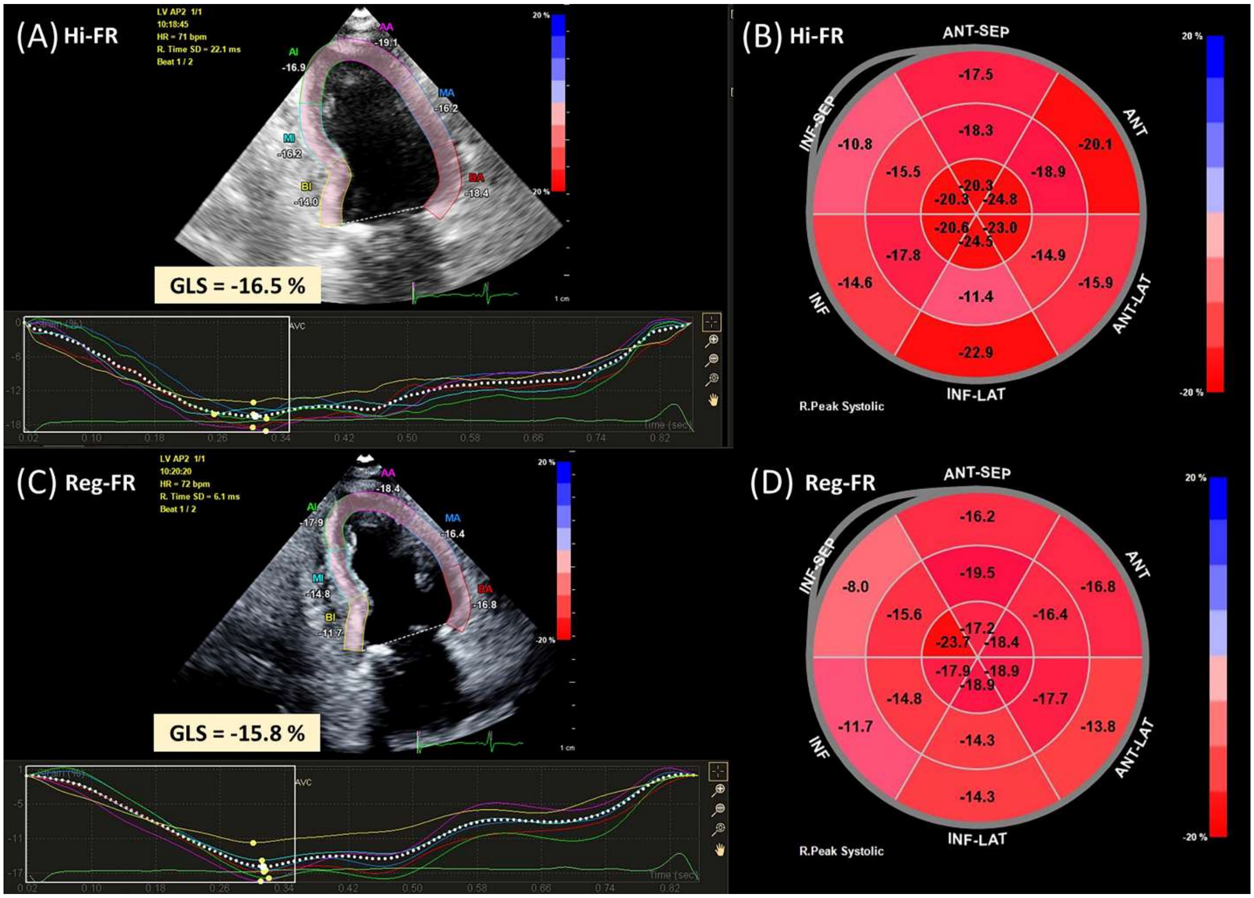
FIGURE LEGENDS

Figure 1. Samples of speckle-tracking analysis. Strain values were evaluated in (A, B) Hi-FR and (C, D) Reg-FR.



Hi-FR, relatively high frame rate; Reg-FR, regular frame rate.

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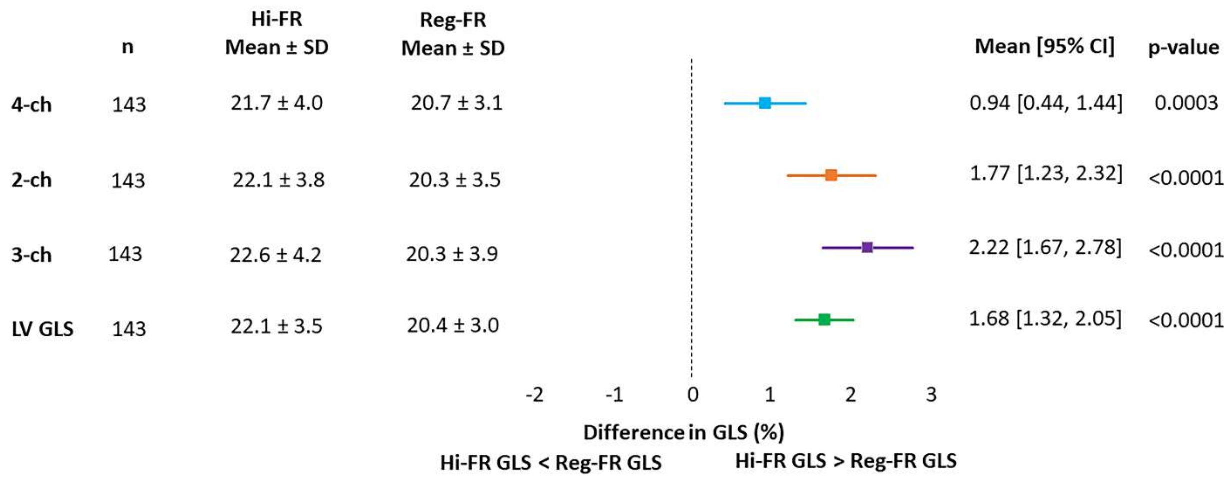
Figure 2. Forest plot showing difference in GLS values measured in Hi-FR vs. Reg-FR.



GLS, global longitudinal strain; Hi-FR, relatively high frame rate; LVEF, left ventricular ejection fraction; Reg-FR, regular frame rate.

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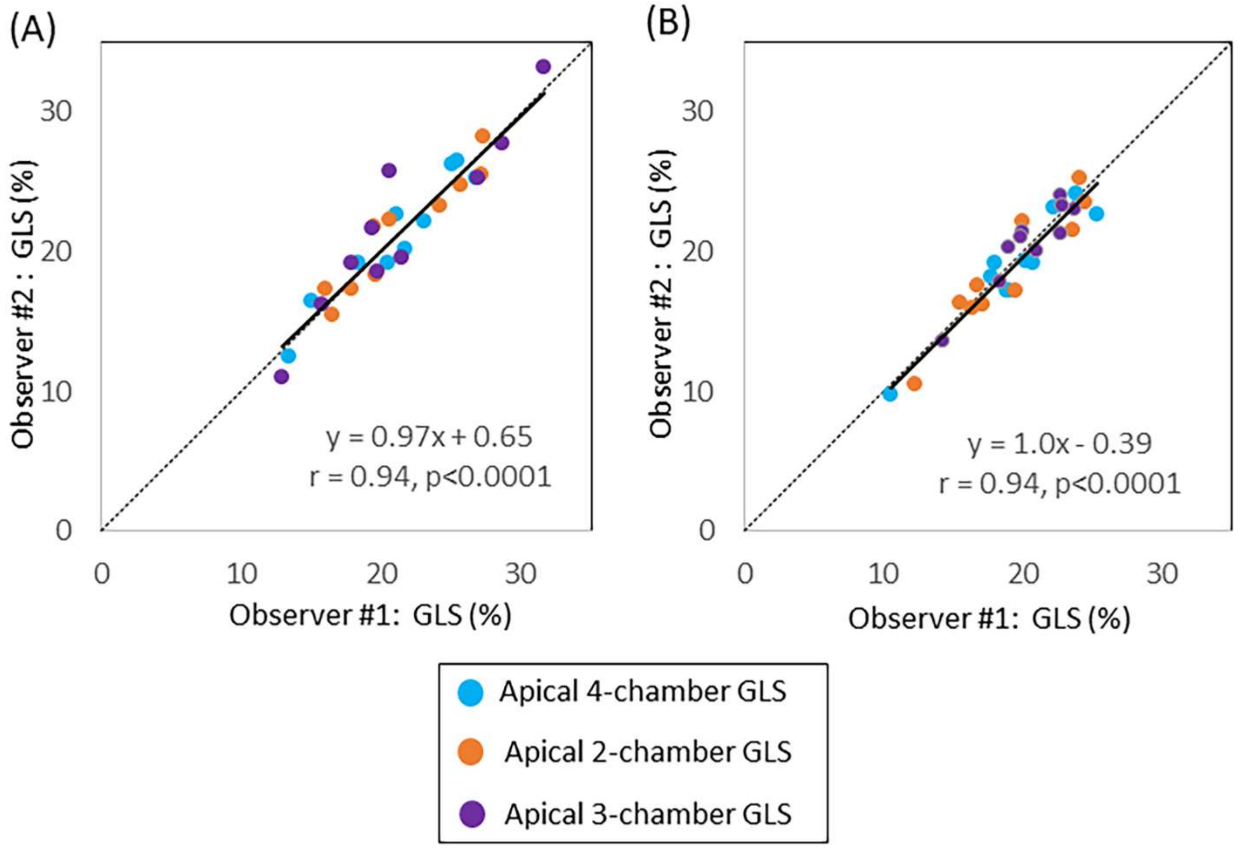
Figure 3. Inter-observer variability in apical 4-, 2-, and 3-chamber views. Linear regression comparing GLS values measured by observer #1 and #2 in (A) Hi-FR and (C) Reg-FR.



GLS, global longitudinal strain; Hi-FR, relatively high frame rate; Reg-FR, regular frame rate.

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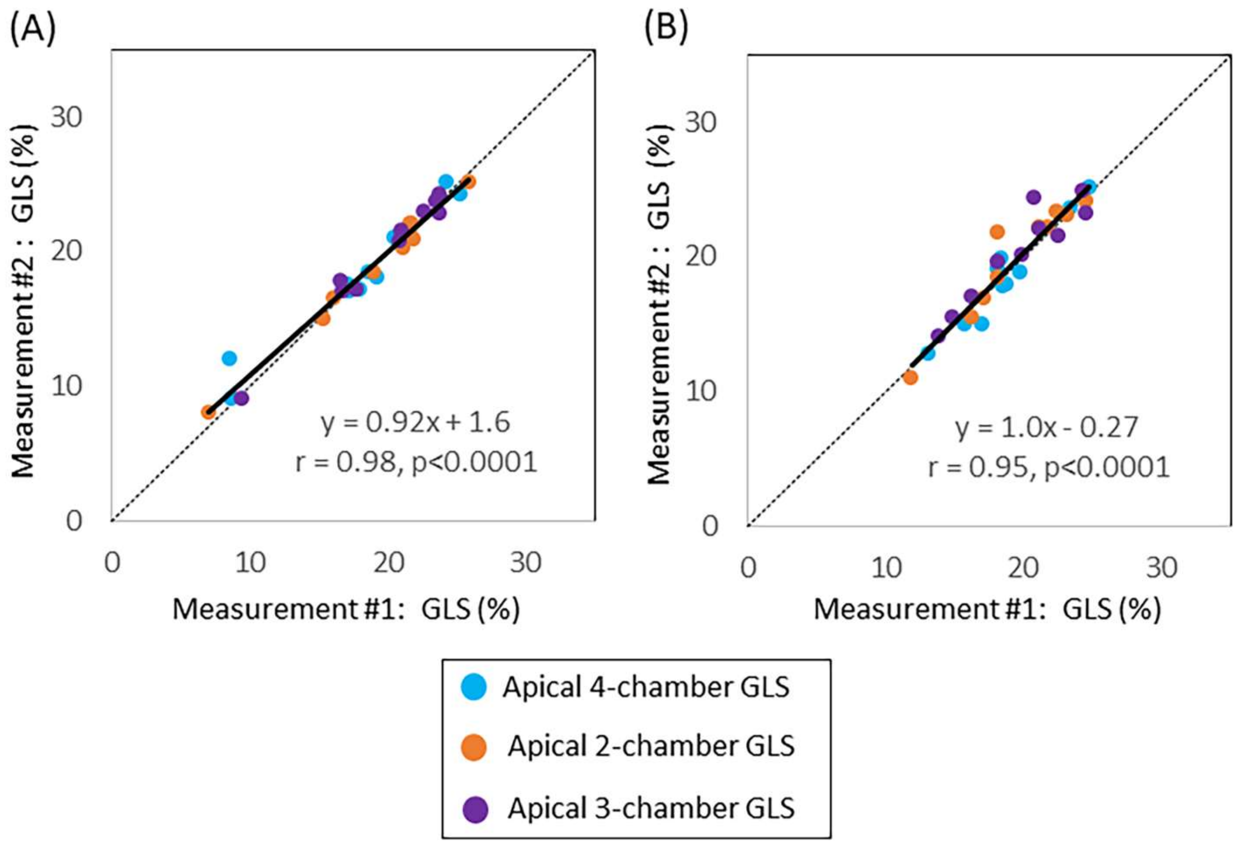
Figure 4. Intra-observer variability in apical 4-, 2-, and 3-chamber views. Linear regression comparing GLS values of 1st and 2nd measurement in (A) Hi-FR and (C) Reg-FR.



GLS, global longitudinal strain; Hi-FR, relatively high frame rate; Reg-FR, regular frame rate.

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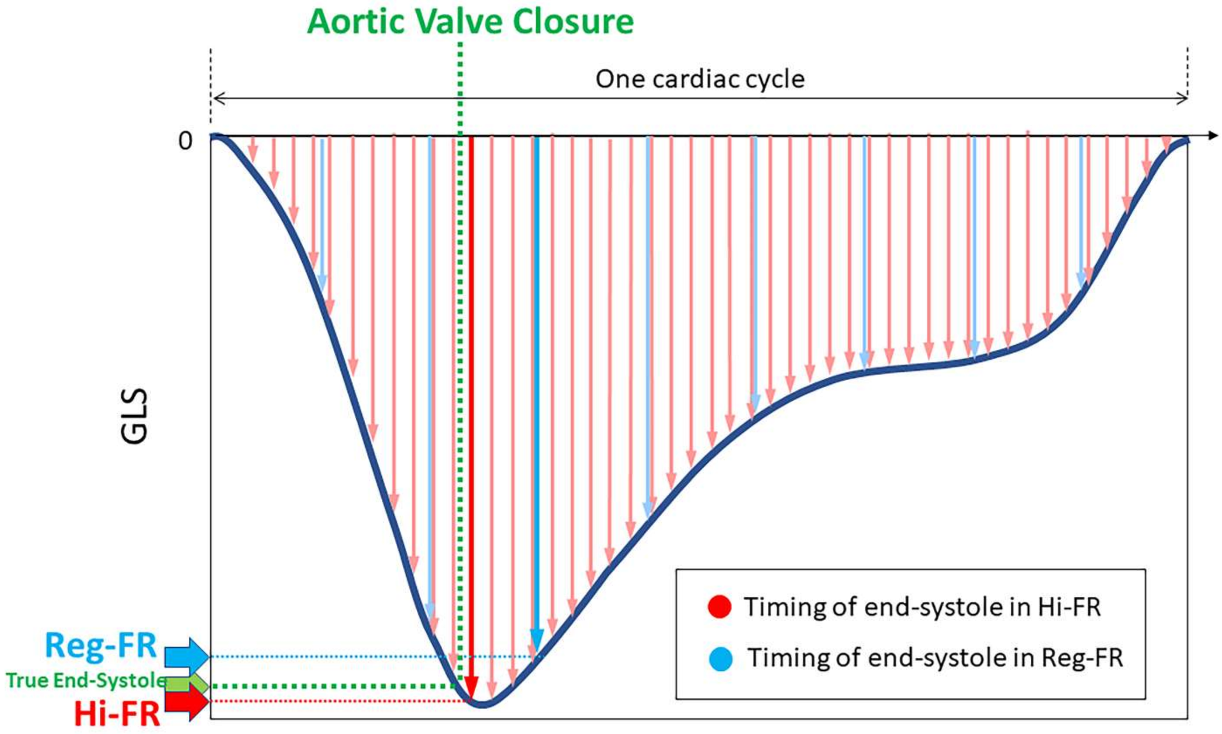
Figure 5. GLS values in Hi-FR and Reg-FR. The dark blue line represents an optimal GLS curve. This scheme demonstrates that the GLS value in Hi-FR is larger and closer to the value at true end-systole compared with the value in Reg-FR.



GLS, global longitudinal strain; Hi-FR, relatively high frame rate; Reg-FR, regular frame rate.

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Table 1. Patient characteristics.

	n=143
Male, n (%)	47 (32.9)
Age, mean±SD (y)	60.1 ± 15.1
Ethnicity	
African American, n (%)	42 (29.4)
Hispanic, n (%)	61 (42.7)
Cocasian, n (%)	10 (7.0)
Asian, n (%)	2 (1.4)
Others, n (%)	28 (19.6)
Hypertension, n (%)	96 (67.1)
Diabetes, n (%)	42 (29.4)
Coronary artery disease, n (%)	25 (17.5)
Hyperlipidemia, n (%)	74 (51.8)
Body mass index, mean±SD (kg/m^2)	1.84 ± 0.23
Systolic blood pressure, mean±SD (mmHg)	133.3 ± 23.2
Diastolic blood pressure, mean±SD (mmHg)	77.2 ± 11.8
Heart rate, mean±SD (beat per minute)	70.6 ± 12.7
LVEF, mean±SD (%)	63.0 ± 5.7