Published in final edited form as:

J Am Soc Echocardiogr. 2013 November ; 26(11): . doi:10.1016/j.echo.2013.07.002.

Reproducibility of Speckle-Tracking Based Strain Measures of Left Ventricular Function in a Community-Based Study

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Abstract

Background—The reproducibility of echocardiographic measurements of myocardial strain, performed in a community-based setting, has not been reported previously.

Methods—We examined the reproducibility of left ventricular (LV) strain measurements in two samples of 20 participants each from the Offspring cohort of the Framingham Heart Study (mean age 63±9 years, 59% women). Two-dimensional speckle tracking-based measurements of global peak LV strain in systole were performed in the apical 4-chamber, apical 2-chamber, and mid-ventricular parasternal short-axis views.

Results—Inter-observer intra-class correlation coefficients (ICC) were 0.84 for all global strain measurements, with average coefficients of variation (CV) of 4% for global longitudinal and circumferential strain, and <8% for global transverse and radial strain. For LV strain measurements performed in each of the 3 views, intra-observer ICCs were 0.91 among time points spanning a total 8-month period. The average CVs were <6% for global longitudinal and circumferential strain, and <9% for global transverse and radial strain. Inter- and intra-observer reproducibility findings were similar in analyses adjusting for frame rate.

Conclusions—We observed excellent reproducibility of global longitudinal and circumferential strain measurements and very good reproducibility of global transverse and radial strain

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Conflicts of Interest/Disclosures

None.

measurements. Taken together, our findings demonstrate the reproducibility of performing echocardiographic strain measurements in a large, epidemiologic community-based setting.

INTRODUCTION

Non-invasive assessments of left ventricular (LV) systolic function have traditionally relied on the measurement of fractional shortening (FS) or, more commonly, estimations of ejection fraction (EF). However, it is well known that both EF and FS have limited sensitivity for characterizing subclinical abnormalities in LV systolic function.¹ Therefore, advanced image analysis techniques have been developed and validated^{2–4} to assess cardiac tissue deformation in multiple planes and, in turn, provide a more sensitive measure of LV performance. When applied to 2-dimensional echocardiography, speckle-tracking based measures of LV deformation (i.e. myocardial tissue strains) have been shown to add incremental prognostic information beyond EF in a variety of settings, including clinical centers and trial cohorts of patients with overt heart failure.^{5–7} Prior studies have examined the reproducibility of echocardiography-based LV strain measures in predominantly small-sized or referral samples.^{8–11} Accordingly, comprehensive data regarding the reproducibility of LV strain measures in a community-based setting are lacking. Therefore, the present study was designed to evaluate the reproducibility of speckle-tracking based LV strain measures in the Offspring cohort of the Framingham Heart Study.

METHODS

Study Sample

The selection criteria and sample selection for the Framingham Offspring Study has been described previously.^{12,13} From 2005 to 2008, a total of 2888 study participants attended their eighth examination cycle and underwent routine M-mode, 2-dimensional, and pulse-wave Doppler echocardiography as part of the standardized Framingham Heart Study clinic visit, using an HP Sonos 5500 ultrasound machine (Philips Healthcare, Andover, MA). Images were acquired according to a protocol that did not specify any procedures for optimizing images for speckle tracking analyses. Because the ability to perform strain-based image measurements is dependent on image quality, all digital images were reviewed for appropriateness for speckletracking based strain analyses. A total of 2844 echo studies were considered appropriate for strain-based image measurements based on the following criteria: images were excluded if greater than 1 segment of dropout was observed for any of the pre-defined 2-dimensional views (apical 2-chamber, apical 4-chamber, or parasternal short-axis at the level of the mid-ventricle), or if the presence of any arrhythmia (e.g. atrial fibrillation, premature atrial or ventricular contractions) was noted during image capture.

From the larger pool of echo studies deemed appropriate for speckle-tracking-based strain analyses, 2 separate sets of 20 studies were randomly selected for reproducibility analyses. The selection of studies for reproducibility was performed by investigators blinded to clinical information. Consecutive echo studies were reviewed for appropriateness for reproducibility based on the criteria described above, in addition to: visualization of the endocardial border in at least 5 of the 6 anatomical segments throughout the cardiac cycle in at least 2 of the 3 predefined views for each echo study: apical 2-chamber (basal-anterior, mid-anterior, apicalanterior, basal-inferior, mid-inferior, and apical-inferior wall segments); apical-4 chamber (basal-anterolateral, mid-anterolateral, apical-lateral, basal-inferoseptal, mid-inferoseptal, and apicalseptal wall segments); and, parasternal short-axis at the mid-ventricular level (mid-anteroseptal, mid-anterior, mid-anterolateral, mid-inferolateral, mid-inferior, and mid-inferoseptal wall segments). As part of a general quality assessment performed prior to selection of images for strain analyses (at the time of image acquisition), and using a simplified ordinal scale (including 4 grades, ranging from 'inadequate' to

'good'), the total set of echo studies selected for reproducibility analyses included 21% that were considered to have 'good' quality 2D images of the LV, 69% 'fair' quality, and 10% 'poor' quality.

All strain measurements were performed by observers blinded to measures performed previously and/or by other observers. The first set of 20 consecutive studies was designated for performing 'baseline' reproducibility analyses, and the second set of 20 consecutive studies was designated for performing 'follow-up' reproducibility analyses over the course of 8 months. We used 2 separate sets of 20 studies to minimize reader recognition of tracings and values (despite being blinded to identifiers) over the course of this reproducibility study. The first set of 20 studies was used to assess inter-observer reproducibility at 'baseline'; the second set of 20 studies was used to assess intraobserver reproducibility at 3 separate occasions over the 'follow-up' period.

All participants provided informed consent prior to attending the examination cycle and the Institutional Review Board of Boston University Medical Center approved the study protocols.

Strain Analyses

Using an off-line analysis program (2D Cardiac Performance Analysis [CPA] v1.1, TomTec Imaging Systems, Unterschleissheim, Germany), previously validated²⁻⁴ speckle-tracking-based analyses of LV function were performed according to a standardized protocol. For all strain analyses, we used a software package (2D CPA) that allows application to images acquired by any type of echo machine, and that has been shown in prior studies to produce strain values that are comparable to other frequently used software packages.¹⁴ Following a 3-month period of training, analyses were performed by 3 sonographers (EO, BL, and PS) in each of the 3 predefined 2-dimensional views: apical 2-chamber (A2C), apical 4-chamber (A4C), and midventricular parasternal short-axis (SAX). The training program involved initial practice on a training set of only good quality images, followed by practice on a training set that included good, fair, and poor quality images. The standardized measurement protocol pre-specified that tracings be performed to optimize myocardial tracking first and foremost, and generation of appropriate strain curves only secondarily. Several tracing techniques were used to optimize myocardial tracking, including: 1) performing traces in the earliest frame with the most optimal visualization of the endocardial border across the maximal number of anatomic segments (this frame was most often end-diastolic for the apical views, and most often mid-systolic for the SAX view); 2) ensuring that the width between endocardial and epicardial tracking lines was not inappropriately narrow or wide at any point in the cardiac cycle; and 3) anchoring basal portions of tracings to the mitral annulus in the apical views, to prevent inappropriate 'straying' of tracing lines over the cardiac cycle.

The primary measurements of interest included the following LV peak systolic strains: global longitudinal and transverse strain in the A2C view; global longitudinal and transverse strain in the A4C view; and, global circumferential and radial strain in the SAX view. Figure 1 shows representative examples of strain curves generated by performing image analyses in each of the 3 views. Frame rates for all analyses were at least 30 and no more than 70 frames per second (fps) for all views: mean 38 ± 5 fps for A2C images, mean 40 ± 7 fps for A4C images, and mean 39 ± 2 fps for SAX images.

Secondary measurements of interest included the regional basal, mid-wall, and apical strains assessed in the longitudinal views. As in prior investigations,¹⁵ basal regional strain was calculated as the average of basal peak strains measured in the A2C (basal anterior and basal inferior) and A4C (basal anterolateral and basal inferoseptal) views; mid-wall regional strain

was calculated as the average of mid-wall peak strains measured in the A2C (mid anterior and mid inferior) and A4C (mid anterolateral and mid inferoseptal) views; and, apical regional strain was calculated as the average of apical peak strains measured in the A2C (distal anterior and distal inferior) and A4C (distal lateral and distal septal) views.

Reproducibility Analyses

Reproducibility analyses were performed in 2 stages over the course of the total measurement period of 12 months (Figure 2). In the first stage, ‘baseline’ inter-reader reproducibility analyses were performed on the first set of 20 echo studies. During this first stage, each reader performed measurements in all 3 views for each of the 20 studies. Inter-observer variability for strain measurements was assessed between the 3 readers for all measurements in all 3 views. In the second stage of ‘follow-up’ measurements, we conducted formal intra-reader reproducibility analyses using a second set of 20 echo studies. For this second set of echo studies, each observer performed repeated measurements for the same view: Reader 1 for the A4C view, Reader 2 for the A2C view, and Reader 3 for the SAX view. Measurements were repeated on 3 separate occasions: the first and second measurements were performed 2 months apart; the second and third measurements were performed 6 months apart (Figure 2). Intra-observer variability for strain measurements was assessed among occasions (i.e. time points of measurements) for each reader.

Statistical Methods

We used several different statistical methods to analyze measurement reproducibility and the sources of variability. In primary analyses, we calculated intra-class correlation coefficients (ICC) for each strain measure, where each ICC value represents the consistency of measurements made by all 3 readers (for inter-observer analyses) or at all 3 occasions (for intra-observer analyses).¹⁶ We also calculated coefficients of variation (CV) for each strain measure, where each CV value represents variability of measurements among all 3 readers for inter-observer analyses or between all 3 occasions for intra-observer analyses.¹⁷ For each strain measure, we also tested the equality of measurement means between readers for inter-observer analyses and between occasions (i.e. time points) for intra-reader analyses, using linear mixed models with fixed effects for reader and for occasion, respectively.¹⁶

In secondary analyses, we also performed pairwise analyses of inter- and intra-observer reproducibility and plotted pairwise differences in strain measurements against pairwise average values in Bland-Altman plots.¹⁸ Because frame rate has been reported to potentially influence reproducibility of strain measurements, particularly at low values of frame rate,^{14,19} we repeated inter-observer and intra-observer reproducibility analyses adjusting for frame rate. We also repeated analyses adjusting for systolic blood pressure and LV mass, considered surrogates of hemodynamic load. The main reproducibility analyses performed for measures of global strain were also repeated for measures of regional strain, as defined above.

All analyses were performed using SAS v9.3 (Cary, NC) and a 2-tailed Bonferroni-adjusted P value threshold of 0.01 (0.05/6) was considered statistically significant.

RESULTS

The participants whose echo images were selected for inclusion in the current study were middle-aged to older adults with an average age of 63.4 ± 9.2 years, and 59% were women. The mean systolic and diastolic blood pressures of the participants were 124 ± 19 and 73 ± 9 mm Hg, respectively; overall, 28% were hypertensive, 13% were smokers, 10% were obese, none had diabetes, and 3% had prevalent cardiovascular disease.

Inter-Observer Reproducibility

The inter-observer reproducibility of global strain measures at baseline for each of the 3 readers and each of the 3 views is shown in Table 1. The average coefficients of variation were 4% for the longitudinal and circumferential strain measures and <8% for the global transverse and radial measures. The inter-observer ICC values were 0.84 for all analyzed measures. Mean values of global strain were not significantly different among readers for measurements in any of the 3 views. In pairwise analyses, coefficients of variation were also better for longitudinal and circumferential strains than for transverse and radial strains (Supplemental Table 1). Figure 3 displays the results of Bland Altman analyses for all global strain measurements in pairwise inter-observer comparisons. Although inter-observer reproducibility was similar across the range of strain values in the study sample (Figure 3), agreement between observers tended to be best for the worst values of strain (i.e. least negative values of longitudinal and circumferential strains, and least positive values of transverse and radial strains). Notably, the range of values in our sample was largest for radial and transverse strains and smallest for longitudinal strains.

Intra-Observer Reproducibility

The intra-observer reproducibility of strain measures performed by the 3 readers over the 'follow-up' period is shown in Table 2. Results of analyzing intra-observer reproducibility of global strain measures at 'baseline' were similar (data not shown). Over the 'follow-up' period, the intra-observer coefficients of variation were 6% for the global longitudinal and circumferential strain measures, and <9% for the global transverse and radial strain measures. For all analyzed measures, intra-observer ICC values were 0.91. Mean values of global strain were not significantly different among occasions for measurements performed by any of the 3 readers. In pairwise analyses, coefficients of variation were also better for longitudinal and circumferential strains than for transverse and radial strains (Supplemental Table 2). Figure 4 shows Bland Altman analyses for intra-observer comparisons of global strain measurements performed at different occasions. Although intra-observer reproducibility was similar across the range of strain values in the study sample (Figure 4), reproducibility tended to be best for the worst values of strain (i.e. least negative values of longitudinal and circumferential strains, and least positive values of transverse and radial strains). Accordingly, as shown in Figure 5, mean (and standard deviation) of global strain measurements performed was stable over the course of the measurement period.

Secondary Analyses

Results of inter-observer and intra-observer reproducibility analyses of global strain measures were not substantially different after adjusting for frame rate (Supplemental Table 3 and Table 4). Inter- and intra-observer reproducibility results were also similar in analyses adjusting for systolic blood pressure and LV mass, considered as surrogate measures of hemodynamic load (data not shown). We also performed inter-observer and intra-observer reproducibility analyses for regional measures of basal, mid-wall, and apical regional strain (Table 3 and Table 4). As reflected by coefficients of variation and ICC, reproducibility was better for mid-wall regional strain measures than for apical and basal strain measures. Measurements of mid-wall regional strain were the most reproducible, with coefficients of variation <7% between readers and between occasions. Overall, mean values of regional strain were not significantly different among readers or among occasions for measurements performed by any of the 3 readers.

DISCUSSION

Speckle-tracking-based measurements of myocardial strain have been used to assess LV function in a variety of cardiac diseases. Whereas prior investigations have examined the

reproducibility of LV strain measurements in either healthy adults or patient referral samples, the present study is the first (to our knowledge) to comprehensively evaluate the reproducibility of performing echocardiographic measures of LV strain in a epidemiologic cohort of ambulatory adults living in the community. In addition to evaluating inter-observer variability at baseline, we also evaluated intra-observer variability over multiple measurement time points spanning an 8-month period.

Overall, we observed very good to excellent reproducibility of global LV strain measurements in our community-based sample, similar to that reported for speckle-tracking-based strain measures performed in selected samples – including healthy young adults¹⁰ and patients with hypertrophic cardiomyopathy.⁸ Specifically, we observed high levels of agreement among and within observers for all measures of peak global LV strain, as represented by high inter- and intraobserver ICC values of 0.84, regardless of the type or orientation (longitudinal or circumferential versus transverse or radial) of the strain measurement. Reflecting the variation in strain measurements that may be seen in a community setting, the wide range of strain values in our study sample, which included individuals with varying burden of cardiovascular risk, may have augmented our reproducibility results despite the use of variable quality images. Indeed, we observed that inter- and intra-observer reproducibility tended to be best for values at the extremes and particularly for values representing worst strain. Because image quality can vary between apical views within the same individual, we analyzed the reproducibility of global peak strains measured in the A2C and A4C views separately, and observed that inter- and intraobserver reproducibility of longitudinal and transverse strains was similar between these views. Notably, reproducibility of global strain measurements was not influenced by variations in image frame rate.

Reproducibility among and within readers was better for the global longitudinal and circumferential strain measures than for the global transverse and radial strain measures. Prior investigations, using either sonomicrometry or non-invasive imaging methods, have also reported higher variability for transverse or radial strain measures, potentially due to factors such as out-of-plane motion of the LV during systole.^{3,4,8,10,20} Transverse or radial strain may also be intrinsically more vulnerable to measurement variability because strains assessed in these orientations represent an aggregate measure of endocardial, mesocardial, and epicardial tissue motion (in either the apical or parasternal views), encompassing both myocardial fiber shortening and global LV torsion in systole. In contrast, longitudinal and circumferential strains are measured at or near the level of the endocardium. Nonetheless, reproducibility of transverse and radial strains was within an acceptable range overall. In our study, the degree to which global longitudinal and circumferential strain measures are more reproducible than global transverse and radial measures may also be related to the fact that the feature tracking software we used is based primarily on endocardial (versus integrated endocardial and epicardial) tracking as well as Lagrangian algorithm (versus natural strains) based estimates. This type of algorithm is similar to many but not all other available feature tracking programs, and such algorithmic differences may have clinical implications. With respect to data acquisition, endocardial-focused tracking is likely more sensitive to alterations in milder forms of subclinical cardiac disease, whereas integrated endocardial and epicardial tracking may be more sensitive to alterations in more advanced disease states.²¹ With respect to data processing, calculated Lagrangian strain values are approximately equal to calculated natural strain values if strains are small, but may substantially differ when strains (i.e. magnitudes of deformation) are large.²² Thus, our observed trends in reproducibility may be dependent on the software algorithm used for strain analyses – as different software packages are known to use different methods for analyses and, for instance, do not rely primarily on Lagrangian calculations and endocardial tracking to estimate longitudinal and circumferential strains.²³

Although there are scant data on the reproducibility of regional strain measures in the published literature, prior studies suggest that regional strain measurements are generally not as reproducible as global strain measurements.^{9,24} In the absence of apical 3-chamber data, we defined regional strain based on available A2C and A4C data and according to levels of the LV myocardium, given the recognized and previously described gradient of increasing strain from the basal to apical levels of the LV.^{25,26} We observed that mid-wall strain measures were more reproducible than apical and basal strain measures, and that intra-observer reproducibility was similar to inter-observer reproducibility of regional strain measures overall. In our study, however, these findings may be related to the fact that our measurement protocol emphasized ensuring endocardial border tracking globally across all segments, rather than by segmental region. Additional studies focused on regional strains are needed to further evaluate their reproducibility.

Several limitations of the present study are worth mentioning. The present investigation was focused on measurement reproducibility, which is only one of several potential sources of variability with respect to LV strain measures. Additional possible sources of variability include within-subject day-to-day, respiratory beat-to-beat, and hemodynamic variability (e.g., alterations in blood pressure or heart rate). To minimize software-related differences as a source of variation, all the strain measurements in the current study were obtained using the same software package; all analyses were also performed on images acquired using the same ultrasound machine. Because different software packages for strain analyses may offer comparable though not consistently similar values,^{14,23,27} the reproducibility results reported herein are at least partly dependent on using the same software for all analyses. Prior studies also suggest that differences in image acquisition between ultrasound machines may contribute to variability in strain measures.²⁷ Given the relatively low prevalence of arrhythmias in our cohort, we did not perform or assess reproducibility of LV strain measures in the setting of arrhythmia. Given the lower mean frame rates of echocardiographic images available in our study sample, we also did not assess reproducibility of LV strain rate measures. Therefore, reproducibility of LV strain-based measures in the setting of chronic arrhythmia, and of LV strain rate measurements, may be the subject of future investigations. Our reproducibility study was conducted in an epidemiological research context with sonographers intensively trained to perform speckle tracking measurements using the TomTec software package and, for intra-observer analyses, specifically trained to perform measurements in a single assigned view. In addition, although the echo studies selected for reproducibility analyses included some fair and poor quality images, the image quality of the studies overall was higher than in the larger cohort based on the criteria used to select these studies. Therefore, whether or not our reproducibility is generalizable to a clinical setting remains uncertain.

In summary, the current study indicates that speckle-tracking based measures of LV strain are reproducible when performed by trained observers in a large epidemiologic cohort study of middle-aged to older men and women living in the community. Although the prevalence of risk factors and disease was lower in our reproducibility sample than in the larger sample of individuals in the source cohort,^{28,29} our sample included individuals with cardiovascular risk factors as well as prevalent cardiovascular disease. Thus, the overall findings of this study provide evidence to support the appropriate use of echocardiographic LV strain measures in ambulatory middle-aged to older adults with variable risk factor burden. Because measurements of radial and transverse strains, and all regional strains, were not as reproducible as longitudinal and circumferential strains, data based on these measurements should be interpreted with caution pending further investigations of their reproducibility in the community.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding

This work was supported by the Ellison Foundation (SC), the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195), and the following grants: K99HL107642 (SC), R01HL093328 (RSV).

REFERENCES

1. Shah AM, Solomon SD. Myocardial deformation imaging: current status and future directions. *Circulation*. 2012; 125:e244–e248. [PubMed: 22249531]
2. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol*. 2006; 47:789–793. [PubMed: 16487846]
3. Langeland S, D'Hooge J, Wouters PF, Leather HA, Claus P, Bijmens B, et al. Experimental validation of a new ultrasound method for the simultaneous assessment of radial and longitudinal myocardial deformation independent of insonation angle. *Circulation*. 2005; 112:2157–2162. [PubMed: 16203928]
4. Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, et al. Two-dimensional strain--a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. *J Am Soc Echocardiogr*. 2005; 18:1247–1253. [PubMed: 16376750]
5. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging*. 2009; 2:356–364. [PubMed: 19808623]
6. Hung CL, Verma A, Uno H, Shin SH, Bourgoun M, Hassanein AH, et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. *J Am Coll Cardiol*. 2010; 56:1812–1822. [PubMed: 21087709]
7. Knappe D, Pouleur AC, Shah AM, Cheng S, Uno H, Hall WJ, et al. Dyssynchrony, contractile function, and response to cardiac resynchronization therapy. *Circ Heart Fail*. 2011; 4:433–440. [PubMed: 21602574]
8. Serri K, Reant P, Lafitte M, Berhouet M, Le Bouffos V, Roudaut R, et al. Global and regional myocardial function quantification by two-dimensional strain: application in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2006; 47:1175–1181. [PubMed: 16545649]
9. Mavinkurve-Groothuis AM, Weijers G, Groot-Loonen J, Pourier M, Feuth T, de Korte CL, et al. Interobserver, intraobserver and intrapatient reliability scores of myocardial strain imaging with 2-d echocardiography in patients treated with anthracyclines. *Ultrasound Med Biol*. 2009; 35:697–704. [PubMed: 19097680]
10. Oxborough D, George K, Birch KM. Intraobserver Reliability of Two-Dimensional Ultrasound Derived Strain Imaging in the Assessment of the Left Ventricle, Right Ventricle, and Left Atrium of Healthy Human Hearts. *Echocardiography*. 2012
11. Rodriguez-Bailon I, Jimenez-Navarro MF, Perez-Gonzalez R, Garcia-Orta R, Morillo-Velarde E, de Teresa-Galvan E. Left ventricular deformation and two-dimensional echocardiography: temporal and other parameter values in normal subjects. *Rev Esp Cardiol*. 2010; 63:1195–1199. [PubMed: 20875360]
12. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*. 1951; 41:279–281. [PubMed: 14819398]
13. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol*. 1979; 110:281–290. [PubMed: 474565]

14. Risum N, Ali S, Olsen NT, Jons C, Khouri MG, Lauridsen TK, et al. Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. *J Am Soc Echocardiogr.* 2012; 25:1195–1203. [PubMed: 22981228]
15. Sun JP, Lee AP, Wu C, Lam YY, Hung MJ, Chen L, et al. Quantification of left ventricular regional myocardial function using two-dimensional speckle tracking echocardiography in healthy volunteers - A multi-center study. *Int J Cardiol.* 2012
16. SAS Institute Inc. SAS/STAT 9.3 User's Guide. Cary, NC: SAS Institute Inc; 2011.
17. Bland JM, Altman DG. Measurement error proportional to the mean. *BMJ.* 1996; 313:106. [PubMed: 8688716]
18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986; 1:307–310. [PubMed: 2868172]
19. Yodwut C, Weinert L, Klas B, Lang RM, Mor-Avi V. Effects of frame rate on three-dimensional speckle-tracking-based measurements of myocardial deformation. *J Am Soc Echocardiogr.* 2012; 25:978–985. [PubMed: 22766029]
20. Reant P, Labrousse L, Lafitte S, Bordachar P, Pillois X, Tariosse L, et al. Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. *J Am Coll Cardiol.* 2008; 51:149–157. [PubMed: 18191740]
21. Borg AN, Ray SG. A unifying framework for understanding heart failure? Response to "Left Ventricular Torsion By Two-Dimensional Speckle Tracking Echocardiography in Patients With Diastolic Dysfunction and Normal Ejection Fraction" by Park SJ et al. *J Am Soc Echocardiogr.* 2009; 22:318–320. author reply 21-2. [PubMed: 19131209]
22. D'Hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, et al. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. *Eur J Echocardiogr.* 2000; 1:154–170. [PubMed: 11916589]
23. Nelson MR, Hurst RT, Raslan SF, Cha S, Wilansky S, Lester SJ. Echocardiographic measures of myocardial deformation by speckle-tracking technologies: the need for standardization? *J Am Soc Echocardiogr.* 2012; 25:1189–1194. [PubMed: 22981227]
24. Hurlburt HM, Aurigemma GP, Hill JC, Narayanan A, Gaasch WH, Vinch CS, et al. Direct ultrasound measurement of longitudinal, circumferential, and radial strain using 2-dimensional strain imaging in normal adults. *Echocardiography.* 2007; 24:723–731. [PubMed: 17651101]
25. Leitman M, Lysiansky M, Lysiansky P, Friedman Z, Tyomkin V, Fuchs T, et al. Circumferential and longitudinal strain in 3 myocardial layers in normal subjects and in patients with regional left ventricular dysfunction. *J Am Soc Echocardiogr.* 2010; 23:64–70. [PubMed: 20122496]
26. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. *Circulation.* 2003; 107:2446–2452. [PubMed: 12743000]
27. Gayat E, Ahmad H, Weinert L, Lang RM, Mor-Avi V. Reproducibility and inter-vendor variability of left ventricular deformation measurements by three-dimensional speckle-tracking echocardiography. *J Am Soc Echocardiogr.* 2011; 24:878–885. [PubMed: 21645991]
28. Cohen KS, Cheng S, Larson MG, Cupples LA, McCabe EL, Wang YA, et al. Circulating CD34(+) progenitor cell frequency is associated with clinical and genetic factors. *Blood.* 2013; 121:e50–e56. [PubMed: 23287867]
29. Harris WS, Pottala JV, Lacey SM, Vasan RS, Larson MG, Robins SJ. Clinical correlates and heritability of erythrocyte eicosapentaenoic and docosahexaenoic acid content in the Framingham Heart Study. *Atherosclerosis.* 2012; 225:425–431. [PubMed: 22727409]

Figure 1.

Representative examples of global left ventricular strain measures obtained from each of the 3 main views: Panel A shows longitudinal and radial strain measured from the A2C view; Panel B shows longitudinal and radial strain measured from the A4C view; and, Panel C shows circumferential and radial strain measured from the SAX view. Colored lines represent strain curves for each of the 6 regional segments over time; black lines represent the global average of strain across the 6 regional segments over time (for each view).

Figure 2.
Timing of baseline and follow-up reproducibility analyses performed. See text for description.

Figure 3.

Bland-Altman plots are shown for inter-observer variability at baseline for measurements made in each of the 3 main views (Panels A through F). The difference between 2 measurements made (per image) is plotted versus the mean value of the 2 measurements made by: Reader 1 compared to Reader 2 (red circles), Reader 1 compared to Reader 3 (blue triangles), and Reader 2 compared to Reader 3 (green cross bars). All values shown are in % units of strain.

Figure 4.

Bland-Altman plots are shown for intra-observer variability, over the course of the measurement period, for measurements made in each of the 3 main views (Panels A through F). The difference between 2 measurements made (per image) is plotted versus the mean value of the 2 measurements made at: Time Point 1 compared to Time Point 2 (red circles), Time Point 1 compared to Time Point 3 (blue triangles), and Time Point 2 compared to Time Point 3 (green cross bars). All values shown are in % units of strain.

Figure 5.

Mean ($\pm$ standard deviation) of measurement values, over the course of the measurement period, are shown for each of the 3 readers: A2C measures of global longitudinal (squares) and transverse (circles) strain for Reader 2 (Panel A), A4C measures of global longitudinal (squares) and transverse (circles) strain for Reader 1 (Panel B), and SAX measures of global circumferential (squares) and radial (circles) strain for Reader 3 (Panel C).

Table 1

Inter-Observer Reproducibility of Global Strain

Global Strain Measure	Measurement in %, Mean (SD)	Within-Subject CV, Mean (SD)	Overall ICC	Tests of Equal Means Among Readers, P value *
A2C longitudinal strain	-23.5 (2.4)	3.3 (1.9)	0.89	0.15
A2C transverse strain	31.6 (7.2)	6.0 (2.6)	0.91	0.42
A4C longitudinal strain	-22.7 (2.3)	4.0 (1.9)	0.84	0.04
A4C transverse strain	32.1 (7.5)	7.3 (5.0)	0.89	0.67
SAX circumferential strain	-31.2 (3.3)	3.0 (2.2)	0.90	0.03
SAX radial strain	43.6 (8.2)	4.7 (8.0)	0.91	0.85

* P values <0.01 are considered statistically significant, accounting for multiple tests.

Table 2

Intra-Observer Reproducibility of Global Strain

Global Strain Measure	Measurement in %, Mean (SD)	Within-Subject CV, Mean (SD)	Overall ICC	Tests of Equal Means Among Occasions, P value *
A2C longitudinal strain	-21.6 (5.1)	6.0 (3.2)	0.92	0.12
A2C transverse strain	30.8 (6.6)	5.8 (2.9)	0.91	0.81
A4C longitudinal strain	-21.6 (4.6)	5.0 (3.0)	0.92	0.95
A4C transverse strain	32.0 (9.2)	6.7 (4.7)	0.93	0.07
SAX circumferential strain	-33.8 (9.3)	3.8 (2.4)	0.98	0.69
SAX radial strain	48.7 (20.3)	8.2 (6.8)	0.95	0.91

* P values <0.01 are considered statistically significant, accounting for multiple tests.

Table 3

Inter-Observer Reproducibility of Regional Strain

Regional Strain Measure	Measurement in %, Mean (SD)	Within-Subject CV, Mean (SD)	Overall ICC	Tests of Equal Means Among Readers, P value [*]
Basal longitudinal strain	−23.6 (3.4)	8.5 (5.6)	0.62	0.05
Midwall longitudinal strain	−19.8 (2.2)	6.3 (3.5)	0.67	0.91
Apical longitudinal strain	−26.0 (2.2)	9.0 (5.2)	0.23	0.04
Basal transverse strain	35.6 (7.4)	11.1 (8.8)	0.69	0.64
Midwall transverse strain	31.6 (6.6)	6.3 (4.3)	0.86	0.43
Apical transverse strain	28.3 (6.9)	13.1 (7.4)	0.72	0.70

^{*} P values <0.01 are considered statistically significant, accounting for multiple tests.

Table 4

Intra-Observer Reproducibility of Regional Strain

Regional Strain Measure	Measurement in %, Mean (SD)	Within-Subject CV, Mean (SD)	Overall ICC	Tests of Equal Means Among Occasions, P value [*]
Basal longitudinal strain	−21.0 (5.3)	8.1 (5.3)	0.89	0.96
Midwall longitudinal strain	−19.1 (4.4)	6.0 (3.2)	0.92	0.98
Apical longitudinal strain	−24.9 (6.1)	11.0 (6.3)	0.75	0.40
Basal transverse strain	35.5 (9.8)	9.5 (6.3)	0.89	0.92
Midwall transverse strain	32.2 (7.4)	6.9 (3.9)	0.91	0.15
Apical transverse strain	26.5 (10.5)	13.3 (8.8)	0.86	0.53

^{*} P values <0.01 are considered statistically significant, accounting for multiple tests.