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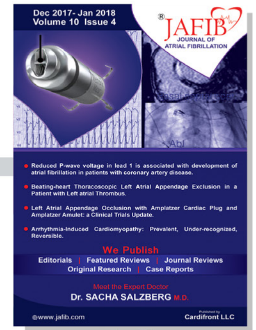


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# Left Ventricular Systolic Function Assessed by Global Longitudinal Strain is Impaired in Atrial Fibrillation Compared to Sinus Rhythm

Bue F Ross Agner[a] , Michael G Katz[b], Zachary R Williams[b], Ulrik Dixen[a], Gorm B Jensen[a], Karl Q Schwarz[b]

*[a]Hvidovre University Hospital, Department of Cardiology, Copenhagen, Denmark.[b]University of Rochester Medical Center, Department of Cardiology, Rochester, New York, USA.*

**Abstract**

**Background:** Atrial fibrillation (AF) is the most common aberrant cardiac arrhythmia. Many AF patients present with symptoms of dyspnea and fatigue, but have normal left ventricular ejection fraction (LVEF).

**Purpose:** To determine the reproducibility of measurements of global longitudinal strain (GLS) and strain rate in patients with AF and examine if the arrhythmia is associated with abnormal LV strain and strain rate independent of age, sex, heart rate, LVEF and LV mass. We hypothesized that AF independently reduces ventricular systolic performance.

**Methods:** The study was conducted as a retrospective analysis of images from 150 randomly selected patients with AF compared to an equal number of subjects with sinus rhythm (SR) matched for age, sex, heart rate, LVEF and LV mass. Half of the patients had normal LVEF (LVEF > 50%) and half had reduced LVEF (LVEF < 50%). GLS and strain rate were measured in each group, as were quantitative LV volumes and standard systolic and diastolic parameters. **Results:** GLS was significantly impaired in patients with AF compared to subjects with SR, both in the overall population (-12.25 ± 4.1% vs. −16.13 ± 4.7%, p<0.0001), in patients with normal LVEF (-14.41 ± 3.9% vs. −19.42 ± 3.1%, p<0.0001) and in patients with reduced LVEF (-10.10 ± 3.1% vs. −12.85 ± 3.5%, p<0.0001). Linear regression and Bland Altman analyses demonstrated good intraobserver and interobserver agreement for measurements of GLS and strain rate parameters even in patients with AF.

**Conclusions:** Measurements of GLS and strain rate parameters are reproducible in patients with AF. Patients with AF have significantly impaired values of GLS when compared to similar patients with SR independent of age, sex, heart rate, LVEF and LV mass.

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the adult population and the prevalence of the arrhythmia is increasing [1]-[3]. AF is often associated with marked elevation in heart rate (HR), which over time may result in a tachycardia mediated cardiomyopathy characterized by reduced left ventricular ejection fraction (LVEF) and congestive heart failure [4]. However, many AF patients present with symptoms of fatigue and dyspnea even without impaired LVEF and without an excessive HR. It is reasonable to assume that both the irregular rhythm and the lack of active left atrial (LA) contraction in the late LV diastole associated with AF may result in reduced force of LV contraction. The most common measure of ventricular systolic function in clinical practice is the LVEF [5]. LVEF is a reliable and reproducible metric, but it has certain limitations, since it depends on the size and shape of the ventricle and on preload and afterload conditions in addition to contractility [6]. Furthermore, since LVEF does not take regional pathophysiological changes into account [7], it can best be described as a macroscopic measure of myocardial contractility that may neglect pathophysiological changes at a microscopic myocardial muscular bundle level. Myocardial strain and strain rate are measures of ventricular performance that have been proven to accurately assess LV myocardial contractility [8]-[10]. Systolic strain is a measure of the deformation of the myocardium that occurs with ventricular contraction, most commonly expressed as the change in base-to-apex longitudinal length of ventricular myocardial segments starting with the onset of ventricular contraction and ending with the closure of the aortic valve. Strain rate represents the speed by which myocardial deformation occurs and is derived from the first derivative of the strain curve [7],[11]. Strain rate is typically expressed as a global systolic and diastolic average with the former occuring at the peak systolic rate of change in ventricular shortening and the latter occuring at the peak rate of lengthening during early ventricular relaxation (corresponding to the E-wave).

The objectives of the present study was to examine the reproducibility of LV strain and strain rate measurements in patients with AF and determine to which extent these measurements are affected by AF independent of age, sex, HR, LVEF and LV mass.

## Key Words

Atrial Fibrillation, Left Ventricular Systolic Function, Global Longitudinal Strain, Systolic Strain, Systolic Strain Rate, Diastolic Strain Rate.

**Corresponding Author**
Bue Ross Agner, MD, PhD Department of Cardiology Hvidovre University Hospital Kettegaard Alle 30 2650 Hvidovre Denmark

## Material and methods

### Study population

The study was conducted as a single-site retrospective analysis of echocardiograms and clinical data collected at the University of Rochester, Rochester, New York, between November 19th, 2007 and

May 30th, 2013. A total of 56,413 echocardiograms were performed during this time period. The inclusion criteria were ECG-documented AF at the time of the imaging procedure and adequate image quality in all standard views. Exclusion criteria included severe cardiac valvular disease, prosthetic valves, pericardial effusion, lack of an analyzable ECG and insufficient image quality (e.g. poor acustic window, frame rate < 45 frames/second etc.). The database of echocardiograms was queried to find two groups of patients depending on whether the codified variable, 'cardiac rhythm', was set to 'atrial fibrillation' (2,364 patients) or 'sinus rhythm' (24,189 patients). A total of 75 patients with AF and normal LVEF (LVEF ≥ 50%) and 75 patients with AF and reduced LVEF (LVEF < 50%) were randomly selected from the database. An identical-sized case-matched control group of 150 patients with SR was then created by matching patients from the SR group on a one-to-one-basis with the AF patients with respect to age, sex, HR, LVEF and LV mass. The study was approved by and conducted under the auspices of the University of Rochester's Ethics Committee. All personally attributable information was anonymized. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

## Echocardiographic Measurements

Echocardiographic imaging was performed according to guidelines from the American Society of Echocardiography (ASE) [12]using equipment capable of storing digital information in RAW format (GE Vingmed Ultrasound AS, Horten, Norway) and analyzed by a core lab using commercially available software (EchoPAC 6.1, GE Vingmed, Horten, Norway). Measurements of traditional systolic and diastolic parameters and standard dimensions were made from the RAW images. In addition, LV diastolic and systolic volumes were measured using the modified Simpson's method averaging the results from the three apical views (apical four-chamber, apical two-chamber and apical three-chamber views). LVEF was calculated from the average LV volumes according to the formula:

LVEF = (end-diastolic volume − end-systolic volume) / end-diastolic volume.

LV mass was calculated using the ASE-recommended formula from LV linear dimensions in the parasternal long axis view[12] and was indexed to body surface area (BSA). Assessment of longitudinal LV strain and strain rate was performed using 2D speckle tracking technique averaging the results from the same 3 apical views that were used to measure LV volume and LVEF.

In patients with AF, echocardiographic data were assessed using the so-called 'index beat method', which has previously been demonstrated to be feasible in patients with AF [17]. Finding cycles with similar RR-intervals in AF patients was not difficult, since cine-loop recordings were available with many more cardiac cycles in AF patients (5 to 10 or even more beats) compared to SR patients (3 beats). The HR used in the analysis of the patients with AF was measured from the RR-interval preceding the analyzed beat and averaged over the 3 views used for LV analysis.

## LV Strain Analysis

2D speckle tracking imaging was used to study LV deformation on standard grayscale images from the three apical views. Using the EchoPAC 6.1 software package, endocardial borders were manually traced on one frame in each view, after which the software automatically tracked the outlined area on subsequent frames by tracking patterns of acoustic markers ("speckles") throughout the cardiac cycle. Myocardial strain was assessed by the change in position of the speckles compared to the initial position. In each of the three apical views 6 segments were analyzed. Accordingly, global systolic strain (GLS) was calculated by averaging the peak systolic values derived from the resulting 18 segments. A positive value indicated myocardial lengthening and a negative value indicated shortening. Examples of the technique are shown in Figure 1. In addition, systolic strain rate (SSR) and diastolic strain rate (DSR) (expressed as 1/s) were calculated as the differential of the strain curve.

## Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical data are summarized as frequencies and percentages. Due to matched pair study design, differences between continuous variables in the AF group and SR group were compared by paired Student's t-tests, and categorical data were analysed by $X_2$test or Fisher's exact test when appropriate. Interobserver and intraobserver variability of strain and strain rate parameters were determined by linear regression (calculating Pearson's correlation coefficients) and Bland Altman analyses. Intraobserver variability was assessed by repeating measurements of strain and strain rate in all segments of images from 20 randomly selected patients, providing 360 measurements of GLS and 60 measurements of SSR and DSR. Interobserver variability was assessed by making a second investigator perform strain and strain rate measurements on images from the same 20 patients.

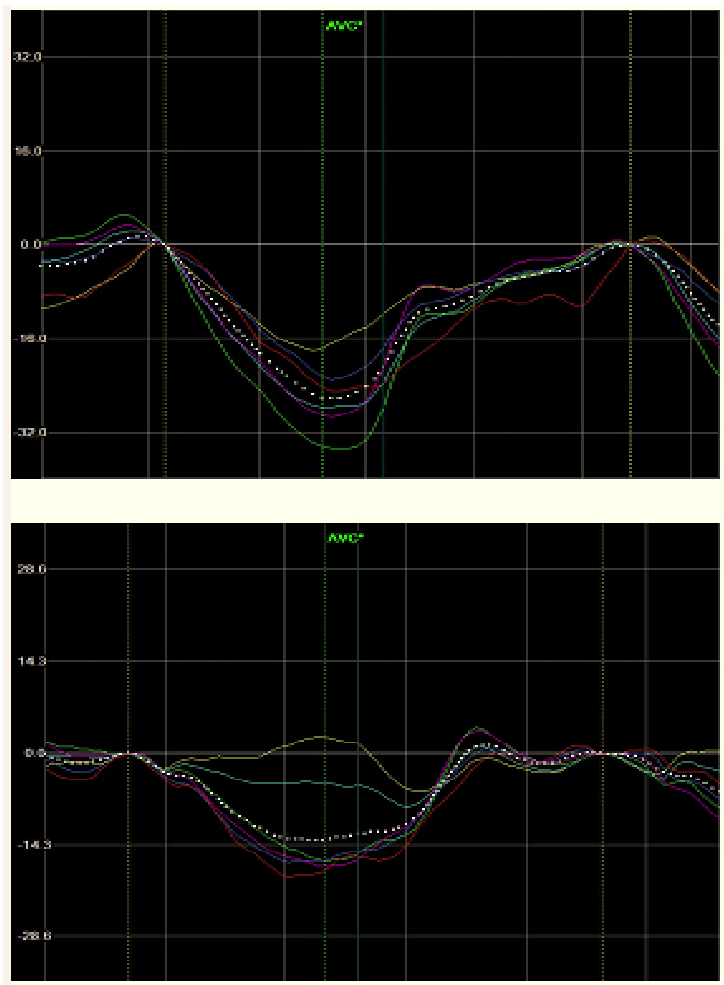


**Figure 1:** Left ventricular global longitudinal strain curves.

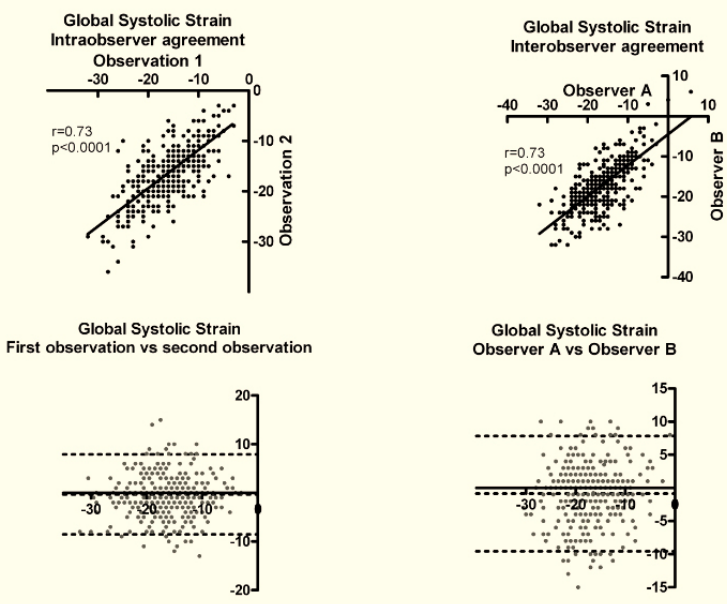


**Figure 2:** Intraobserver and interobserver variability. Upper panel: Linear relationship between measurements of Global Systolic Strain (GLS). Intraoberserver variability (left) and interobserver variability (right). Lower panel: Bland Altman plots for intraobserver (left) and interobserver variability (right) of GLS."

Statistical analyses were performed with the use of commercially available packages (SAS 9.3, SAS System, Cary, NC, USA and GraphPad Prism 4.0 GraphPad Software, San Diego, CA, USA). All p-values were two-sided, and a p-value < 0.05 was considered significant.

**Table 1:** Patient characteristics

| | Preserved LVEF | | | Reduced LVEF | | |
|---|---|---|---|---|---|---|
| | (LVEF>50%) | | | (LVEF<50%) | | |
| | SR | AF | p | SR | AF | p |
| | (n=75) | (n=75) | | (n=75) | (n=75) | |
| Age (years) | 72.7± 12.6 | 72.7± 12.5 | 0.995 | 72.2 ± 13.1 | 72.8 ±13.1 | 0.762 |
| Sex (% male) (n) | 60.0 (45) | 60.0 (45) | 1.000 | 60.0 (45) | 60.0 (45) | 1.000 |
| BMI (kg/m2) Normal | 28.5 ± 5.5 | 29.5 ± 6.2 | 0.364 | 27.4 ± 5.2 | 27.8 ± 5.1 | 0.780 |
| BSA (m2) | 1.92 ± 0.2 | 2.0 ± 0.3 | 0.050 | 1.92 ± 0.2 | 1.98 ±0.3 | 0.261 |
| Heart Rate(bpm) | 83.4 ± 15.9 | 86.7 ± 19 | 0.263 | 86.1 ± 18.5 | 87.9 ±20.4 | 0.579 |
| Hypertension(% (n) | 81.3 (61) | 76.0 (57) | 0.550 | 77.3 (58) | 70.7 (53) | 0.457 |
| Diabetes (%) (n) | 30.7(23) | 32.0 (24) | 1.000 | 36.0 (27) | 32.0 (48) | 0.731 |
| Previous stroke/ TCI (%) (n) | 14.7 (11) | 24.0 (18) | 0.214 | 10.7 (8) | 16.0 (12) | 0.472 |

Data are presented as mean ± standard deviation or as % (n) unless otherwise stated. BMI: body mass index, BSA: body surface area, TCI: transitory cerebral ischemia

## Results

Patient characteristics are given in Table 1. Echocardiographic parameters of the AF and SR groups are given in Table 2. In the AF group mean duration of AF was 2.5 ± 0.8 years. In accordance with clinical expectations, the LA volume was significantly larger in the AF group than in the SR group. Linear regression analysis

**Table 2:** Echocardiographic parameters in the SR population and AF population

| | Preserved LVEF (LVEF>50%) | | | Reduced LVEF (LVEF<50%) | | |
|---|---|---|---|---|---|---|
| | SR (n=75) | AF (n=75) | p | SR n=75 | AF (n=75) | p |
| LVEF (%) | 57.2 ± 5.0 | 58.0 ± 5.1 | 0.428 | 37.5 ± 7.4 | 36.6 ± 7.9 | 0.247 |
| LV mass index (g/m2) | 121.0 ± 29.4 | 127.4 ± 36.4 | 0.2086 | 133.9 ± 31.1 | 138.0 ± 35.0 | 0.548 |
| LVED volume (ml) | 99.8 ± 42.1 | 112.3 ± 29.9 | 0.030 | 121.1 ± 46.0 | 142.3 ± 47.3 | 0.007 |
| LAVI (ml/m2) | 30.1 ± 10.4 | 49.4 ± 18.7 | <0.0001 | -12.85 ± 3.5 | -10.10 ± 3.1 | <0.0001 |
| GLS (%) | -19.42 ± 3.1 | -14.41 ± 3.9 | <0.0001 | -12.85 ± 3.5 | -10.10 ± 3.1x | <0.0001 |
| SSR (s-1) | -1.08 ± 0.3 | -0.90 ± 0.2 | <0.0001 | -0.72 ± 0.3 | -0.61 ± 0.2) | 0.0002 |
| DSR (s-1) | 14.7 (11) | 1.30 ± 0.4 | 0.113 | 0.88 ± 0.3 | 0.86 ± 0.3 | 0.587 |

Data are presented as mean ± standard deviation. LVED volume; left ventricular end diastolic volume, LVES volume: left ventricular end systolic volume, LVEF: left ventricular ejection fraction, LAVI: left atrial volume index, GLS: global longitudinal strain, SSR: systolic strain rate, DSR: diastolic strain rate

demonstrated good intraobserver and interobserver agreement for GLS, SSR and DSR. For intraobserver variability, the Pearson's correlation coefficients were 0.73, 0.70 and 0.89 for GLS, SSR and DSR, respectively, and Bland Altman analyses gave mean differences of –0.31 ± 4.19%, -0.05 ± 0.17 $s^{-1}$ and 0.05 ± 0.23 $s^{-1}$ for GLS, SSR and DSR, respectively (Figure 2).

In the overall study population, GLS was significantly impaired in the AF group compared to the SR group (-12.25 ± 4.1% vs. –16.13 ± 4.7%, p<0.0001) (Figure 3).

Similarly, in the subgroup of patients with preserved LV systolic function (LVEF ≥ 50%), GLS was significantly impaired in the AF group compared to the SR group (-14.41 ± 3.9% vs. –19.42 ± 3.1%, p<0.0001) (Figure 3), and the same was the case in the subgroup of patients with reduced LV systolic function (LVEF < 50%), where GLS was also significantly impaired in the AF group compared to the SR group (-10.10 ± 3.1% vs. –12.85 ± 3.5%, p<0.0001) (Figure 4). For SSR, absolute values were significantly lower in the overall AF population compared to the the overall SR population (-0.76 ± 0.2 $s^{-1}$ vs -0.90 ± 0.3 $s^{-1}$, p<0.00001) [Figure 3]. The same was the case in the subgroups with preserved LVEF (-0.90 ± 0.2 vs. –1.08 ± 0.3 $s^{-1}$, p<0.0001) and the subgroups with reduced LVEF (-0.61 ± 0.2 s-1 vs. –0.72 ± 0.2 $s^{-1}$, p=0.0002) (Figure 4).

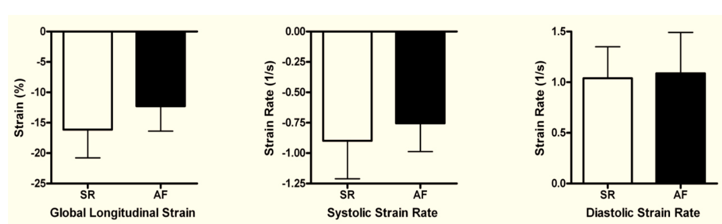


**Figure 3:** Atrial fibrillation vs. sinus rhythm. Comparison of strain and strain rate measurements in the overall study population.Differences in global longitudinal strain (GLS) (left), systolic strain rate (SSR) (middle) and diastolic strain rate (DSR) (right) between patients with atrial fibrillation (AF) and patients with sinus rhythm (SR) for all ranges of left ventricular ejection fraction (LVEF).

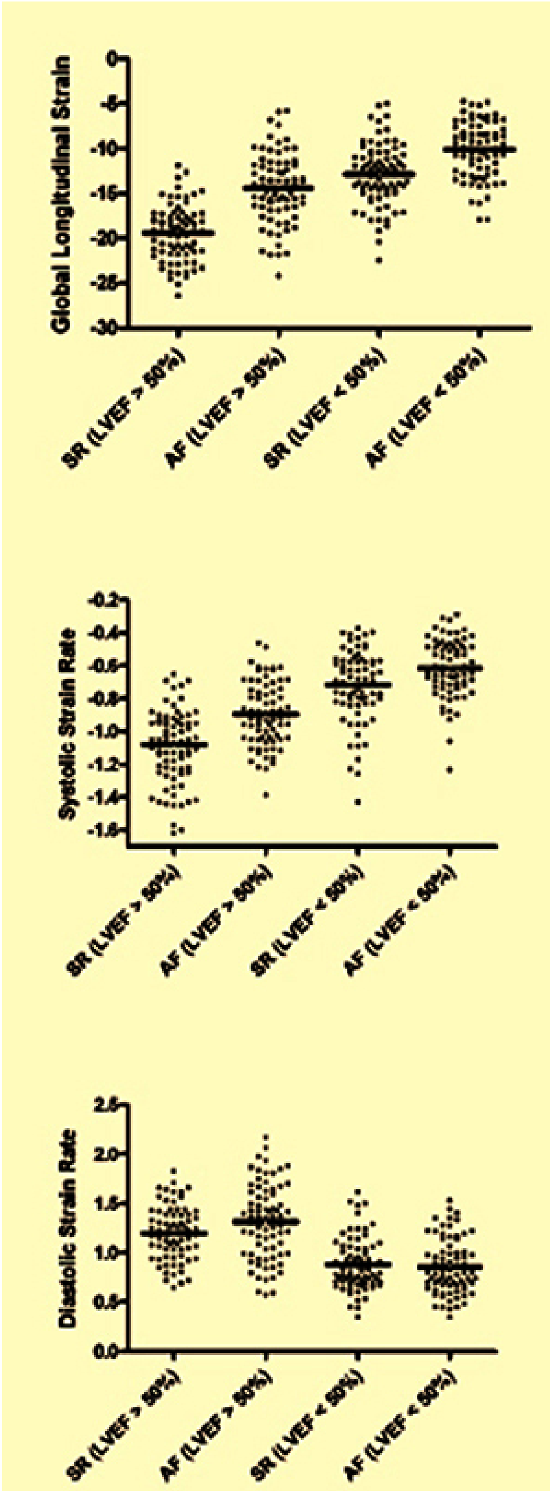


**Figure 4:** Atrial fibrillation vs. sinus rhythm. Comparison of strain and strain rate measurements in subgroups with preserved and reduced left ventricular ejection fraction (LVEF), respectively.Differences in values of global systolic strain (GLS) (top), systolic strain rate (SSR) (middle) and diastolic strain rate (DSR) (bottom).

DSR values were marginally larger in the overall AF group than in the SR group, but the difference was not statistically significant (1.09 ± 0.41 s-1 vs. 1.04 ± 0.31 s-1, p=0.147) (Figure 3). Neither were the results significantly different between the subgroups with preserved LVEF (1.30 ± 0.37 s-1 vs. 1.20 ± 0.27 s-1, p=0.113) or the subgroups with reduced LVEF (0.86 ± 0.28 s-1 vs. 0.88 ± 0.27 s-1, p=0.587) (Figure 4).

## Discussion

Assessment of strain based on 2D speckle tracking enables detection of more subtle abnormalities in LV contractility than can be appreciated by measuring LVEF. 2D strain assessment allows reliable distinction between active contraction and passive motion [13],[14]. Hence, it can be used to assess regional LV function in addition to global function. Due to the beat-to-beat variability associated with AF, analysis of myocardial strain has only been performed in relatively few studies of patients with AF [15],[17]. 2D speckle tracking strain imaging provides angle-independent evaluation of LV systolic function in 4 directions: radial, circumferential, longitudinal and rotational. The most reproducible of these strain measurements is longitudinal strain, which has been shown to be feasible in the early detection of contraction abnormalities in cardiac diseases such as hypertrophic cardiomyopathy with preserved LVEF [8].

The greater sensitivity of longitudinal strain compared to other strain modalities is thought to be caused by the fact that longitudinal fibers located in the subendocardium may be the most susceptible to pathological changes [18]-[20].

In the present study we have demonstrated that measurements of GLS and the derived parameters of SSR and DSR are reproducible even in patients with AF. Moreover, we have demonstrated that GLS is significantly impaired in AF compared to SR independent of age, sex, HR, LVEF and LV mass. These findings suggest that the extent of myocardial dysfunction is greater in patients with AF than in comparable subjects with SR, which indicates that the irregular LV filling associated with AF results in subclinical alterations in LV contractility that may precede deterioration of overall LV systolic function.

## Limitations

Limited clinical information about the patients in the database was available, e.g. about the type of AF (paroxysmal, persistent, permanent) the patients had, as well as information about confounding factors, such as exposure to chemotherapy and/or radiation therapy. This lack of clinical information is an important limitation to the study, since these factors may well have had an impact on measurements of strain and strain rate. In addition, LA volumes were significantly larger in the AF group than in the SR group, which is consistent with clinical expectations and with findings from previous imaging studies [25]. However, these differences in LA volume imply that LA pressure was be higher in AF compared to SR, which combined with the lack of atrial contraction may have resulted in the finding of a slightly higher mean DSR value in the AF group compared to SR. Further investigation is needed to investigate the diastolic function abnormalities in AF patients taking the LA pressure and diastolic filling interval into account. Finally, differences in medication between the AF and SR group, especially in the use of beta blockers, could potentially contribute to the observed findings, since beta blockers are well known to alter preload and afterload conditions.

## Conclusion

Measurements of GLS, SSR and DSR are reproducible in patients with AF. Patients with AF have significantly impaired values of GLS when compared to similar patients with SR independent of age, sex, HR, LVEF and LV mass.

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The authors have no conflicts of interest.

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