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CLINICAL RESEARCH

Multilayer global longitudinal strain in patients with cancer: A comparison of two vendors

Strain longitudinal global *multicouche chez des patients pris en charge pour un cancer : une comparaison de 2 vendeurs*

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KEYWORDS
Echocardiography;
Cardio-oncology;
Myocardial layers;
Speckle tracking;
Intervendor variability

Summary
Background. — Global longitudinal strain (GLS) has several sources of variation. Strain multilayer tracking is a new tool that has not yet been validated in clinical practice.
Aim. — The purpose of this study was to investigate intervendor variability when measuring multilayer strain in patients receiving chemotherapy for cancer.
Methods. — Patients receiving chemotherapy for cancer, who were referred for echocardiography, were included prospectively. First, the same operator performed two-dimensional echocardiography on each patient using the Vivid E9™ (General Electric, Fairfield, CT, USA) and the ACUSON SC2000™ (Siemens, Munich, Germany) ultrasound systems. Second, we assessed myocardial deformation by using their respective speckle-tracking software. Third, we compared absolute values of GLS for the two vendors in each apical view (four-, three- and two-chamber) and for each layer (endocardial, mid-myocardial and epicardial).

Abbreviations: 2D, two-dimensional; CCC, concordance correlation coefficient; GE, General Electric; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction.

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Results Eighty patients with cancer were included prospectively between February and June 2015. For a given vendor, GLS values decreased from the endocardial layer to the epicardial layer. For a given view, GLS values obtained with the ACUSON SC2000 platform were systematically lower than those obtained with the Vivid E9 platform ($P < 0.0001$). We observed a significant difference between the two platforms, irrespective of the layer, interlayer gradient or chamber view considered ($P < 0.0001$).
Conclusions. — There was poor agreement for layer-specific strain evaluation between the Vivid E9 and ACUSON SC2000 platforms, using their dedicated software for strain multilayer assessment. These results suggest that, in clinical practice, the same system and software from the same vendor should be used for longitudinal follow-up.

MOTS CLÉS
Échocardiographie ;
Cardio-oncologie ;
Couches myocardiques ;
Speckle tracking ;
Variabilité intervendeur

Résumé
Contexte. — Le *strain longitudinal global* (SLG) a de multiples causes de variabilité. Le strain multicouche mesuré par la méthode de *speckle tracking* est un outil n'ayant pas encore été validé dans la pratique clinique.
Objectif. — L'objectif de cette étude était d'évaluer la variabilité intervendeur de la mesure du strain multicouche chez des patients suivis pour une néoplasie recevant des chimiothérapies.
Méthodes. — Les patients recevant une chimiothérapie dans le cadre du traitement de cancer, adressés pour une échographie cardiaque ont été inclus de manière prospective. Premièrement, le même opérateur a réalisé une échographie 2D à chaque patient en utilisant 2 échographes, le Vivid E9™ (General Electric, Fairfield, CT, États-Unis) et l'ACUSON SC2000™ (Siemens, Munich, Allemagne). Deuxièmement, nous avons évalué la déformation myocardique en utilisant leur logiciel respectif de speckle tracking dédié à la mesure du strain multicouche. Troisièmement, nous avons comparé les valeurs absolues de SLG des 2 constructeurs dans chaque incidence apicale (4-, 3- et 2- cavités) et pour chaque couche (endocarde, couche myocardique moyenne et épicarde).
Résultats. — Quatre-vingt patients traités pour un cancer ont été inclus prospectivement entre février et juin 2015. Pour chaque constructeur, les valeurs de SLG diminuaient de la couche endocardique vers la couche épicardique. Pour une incidence donnée, les valeurs de SLG avec la machine ACUSON SC2000 étaient systématiquement plus faibles que celles obtenues avec la machine Vivid E9 ($p < 0{,}001$). Nous avons observé une différence significative des valeurs de strain multicouche entre les 2 constructeurs que l'on considère la couche myocardique, le gradient intercouche ou l'incidence apicale ($p < 0{,}0001$).
Conclusion. — Il y avait une faible concordance entre le Vivid E9 et l'ACUSON SC2000 en utilisant leur logiciel dédié pour l'évaluation du strain multicouche. Ces résultats suggèrent que pour la pratique clinique, la même machine et logiciel du même constructeur soient utilisés pour le suivi des patients.

Background

Recent guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend the use of global longitudinal strain (GLS) and cardiac troponin I for the early identification of cancer therapy-related cardiac dysfunction, particularly in patients receiving treatment with anthracyclines and/or trastuzumab [1]. The GLS value is also considered a predictor of mortality in patients with cancer who are receiving chemotherapy [2]. However, the robustness of speckle-tracking echocardiography in routine clinical practice has been questioned because of intervendor variability [3—6]. Several factors, such as anthropometric variables (age, sex) and haemodynamic variables (blood pressure), are also known to be a source of variability when GLS values are compared between different vendors [7—11]. Speckle-tracking software might lead to significant changes in GLS values, which affect intervendor reproducibility. Consequently, consensus between manufacturers and clinicians has been established to reduce intervendor variability for transmural GLS [12].

Multilayer strain is a recent tool that is designed to improve evaluation of myocardial deformation when assessing layer-specific strain [13,14]. So far, measurement of multilayer strain has been assessed in several

clinical settings, especially in the evaluation of myocardial ischaemia. Endocardial function was more affected than epicardial function in patients with significant coronary disease [15]. More recently, Ejlersen et al. showed that three layer-specific variations of GLS values added independent predictive value to the diagnosis of existing coronary artery disease in a patient with chest pain [16]. However, there is no recommendation to use strain multilayer in daily clinical practice. Few studies have provided data on normal values [17] and reproducibility [18]. Moreover, there is no study assessing intervendor variability. In fact, it appears important to provide reproducible measures before the use of this technique becomes widespread.

This study was designed to compare two different commercially available cardiac ultrasound platforms, and their manufacturer-specific speckle-tracking echocardiography software, for quantification of multilayer myocardial strain in patients with cancer.

Methods

Population

Between February and June 2015, 91 consecutive patients with cancer included in a phase I protocol were referred to our department for cardiac evaluation, before receiving oral molecular targeted agents. Physical examination, cardiovascular risk factors, treatments and an electrocardiogram were recorded at entry into the study. Informed consent to participate in the study was obtained from all subjects.

Two-dimensional echocardiography

Standard two-dimensional (2D) echocardiography was performed using two commercially available ultrasound machines: the VIVID E9™ (General Electric [GE], Fairfield, CT, USA) and the ACUSON SC2000™ (Siemens, Munich, Germany), with their dedicated probes (the M5S-D/4V probe for the VIVID E9 and the 4V1/4Z1 probe for the ACUSON SC2000). All examinations were performed by the same experienced echocardiographer on the two machines.

To reduce variability caused by haemodynamic conditions, and for a given patient, examinations were acquired on the two platforms during a 45-minute interval that began with the first acquisitions made on the first echocardiographic platform and ended when the acquisition made on the second platform had been completed. The order of examinations on each platform was reversed for every 20 examinations.

Chamber quantification was assessed according to current guidelines [19]. Left ventricular (LV) size and mass were determined using M mode in the parasternal long-axis view. Mitral inflow was obtained by pulsed-wave Doppler echocardiography (four chamber) and the mitral annulus velocities were obtained from the septal and lateral annulus by spectral Doppler tissue imaging. Aortic flow was recorded using pulsed Doppler echocardiography. Left atrial volume measurement was realized in two- and four-chamber views using Simpson's biplane method.

LV ejection fraction (LVEF) was calculated using Simpson's biplane method in the apical four- and two-chamber views.

Acquisition of speckle tracking

GLS multilayer measurements with the GE platform (VIVID E9)

Cine loops were digitally recorded in apical four-, three- and two-chamber views, with high frame rates (> 50 frame/s), and were analysed using commercially available software (Automated Function Imaging, EchoPAC; GE Healthcare, Little Chalfont, UK). All the data were analysed offline using the fully functional EchoPAC version for multilayer strain analysis (EchoPAC BT13; GE Healthcare).

The region of interest for measuring multilayer GLS in each view was obtained by tracing the endocardium. The software algorithm automatically segmented the LV plane into equidistant segments. The region of interest was adjusted manually, if necessary. End-systole was defined manually as aortic valve closure in the apical long-axis view. The software allowed LV longitudinal strain analysis of two different layers: endocardial and epicardial. Mid-myocardial strain was the average of the endocardial and epicardial layer (Fig. 1). Tracking quality was controlled before validation, using visual evaluation, quality of the strain curves and quality assessment, according to the Automated Function Imaging software. Segments with impaired quality of tracking were excluded from the analysis. Peak systolic strain measurements were expressed as absolute values, using an 18-segment LV model.

GLS multilayer measurements with the Siemens platform (ACUSON SC2000)

Cine loops were recorded digitally in apical four-, three- and two-chamber views, with high frame rates (> 50 frame/s), for later offline analysis, using a dedicated software package (Velocity Vector Imaging VB10D, Siemens). The endocardium was traced manually on each view, and the software defined the epicardium, allowing the region of interest to be determined within the myocardium. The software allowed LV longitudinal strain analysis of two different layers: endocardial and epicardial. Mid-myocardial strain was the average of the endocardial and epicardial layers. Tracking quality was evaluated by assessing the strain curves for specific layer (Fig. 2). Tracking was adjusted manually, if necessary. Segments with impaired quality of tracking were excluded from the analysis. Peak systolic strain measurements were expressed as absolute values using an 18-segment LV model.

Definitions

GLS according to layer

On each platform, GLS was obtained for each layer (endocardial, mid-myocardial and epicardial) and for each apical view. For a given view, mean GLS was calculated as the sum of the six segmental strain values of a given layer, divided by 6. Thus, GLS could be measured in a given layer

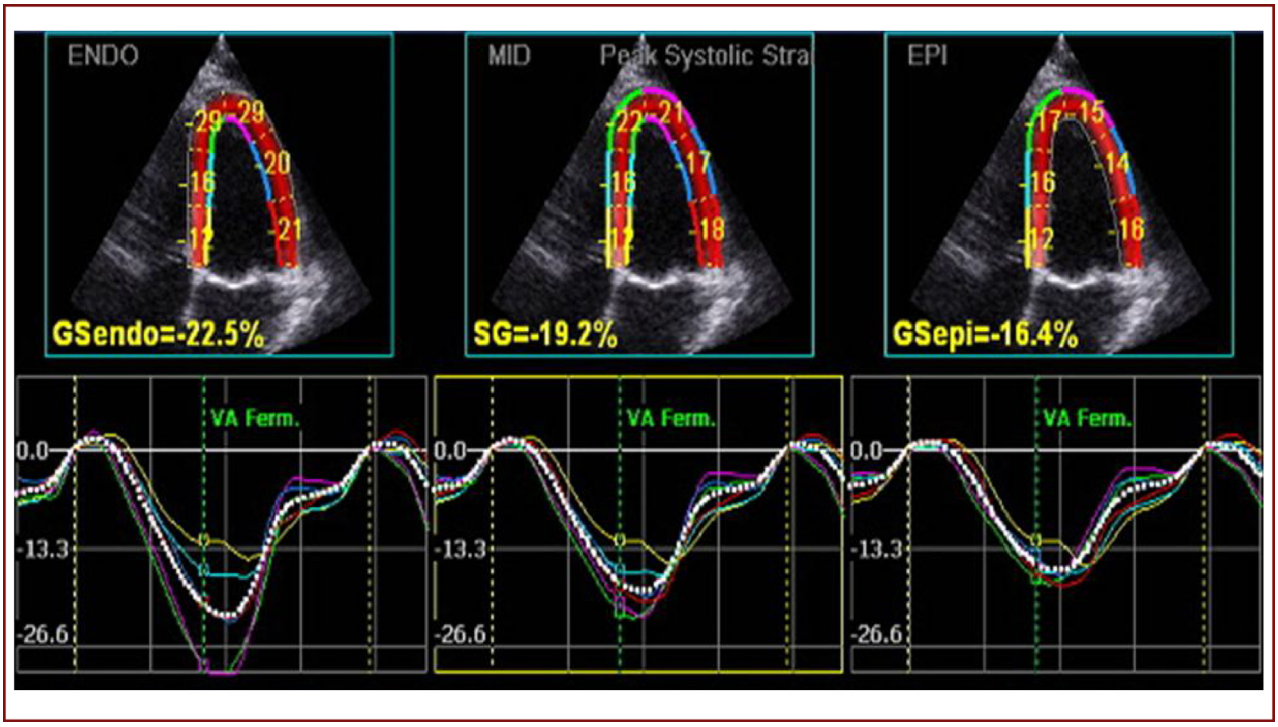

Figure 1. Global strain of endocardial, mid-myocardial and epicardial layers in apical four-chamber view using EchoPAC software.

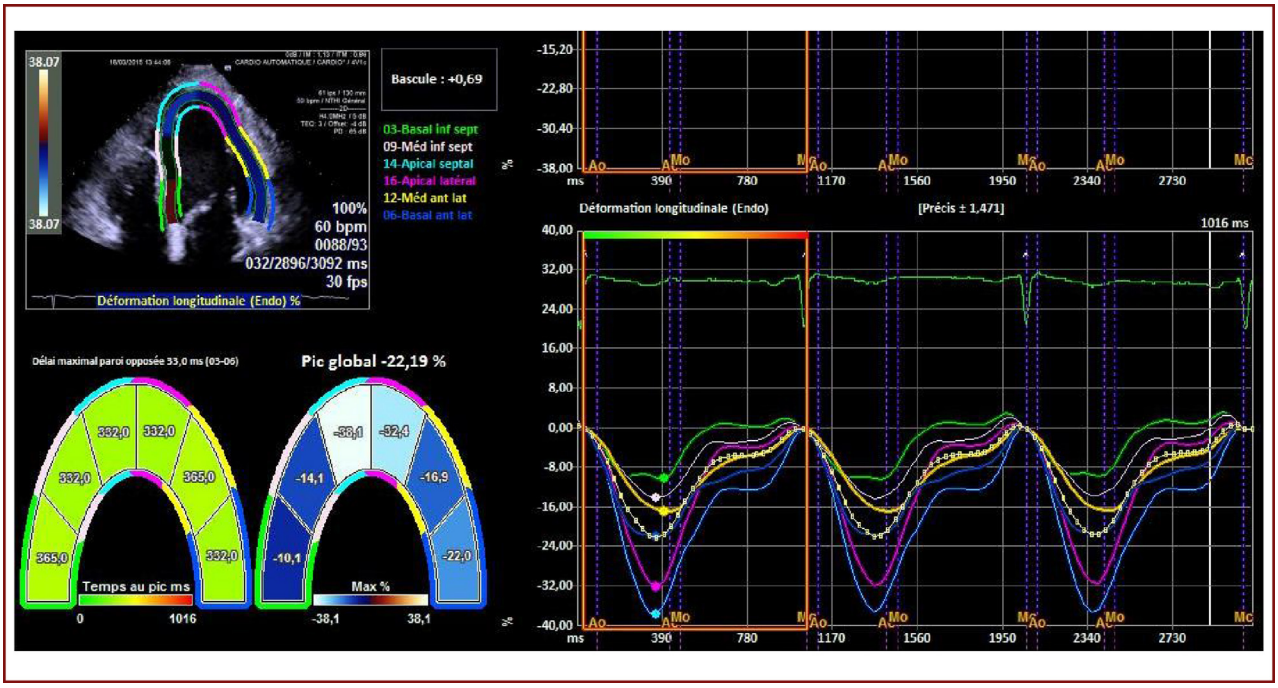

Figure 2. Global strain of endocardial layer in apical four-chamber view using Velocity Vector Imaging software.

(endocardial, mid-myocardial or epicardial) and in a given view (apical four-, three- and two-chamber).

GLS according to chamber view

On each platform, GLS according to a given chamber view was defined as the average of the values of GLS for each layer, divided by 3. Thus, the average GLS could be defined in the apical four-, three- and two-chamber views.

Interlayer gradient of GLS

For each platform, the interlayer gradient of GLS was defined as the difference in GLS value between two layers in a given view. The interlayer gradient of GLS could be

calculated between the endocardial and mid-myocardial layers, between the endocardial and epicardial layers and between the mid-myocardial and epicardial layers.

Observer variability

Twenty randomly assigned patients were analysed again by the same observer (Y.A.), 1 week after the initial analysis, using the GE and Siemens software, to assess intraobserver variability for GLS, LVEF in 2D and end-diastolic and end-systolic volumes. Data from the same patients were analysed with the two software programs by a second observer (S.E.), for evaluation of interobserver variability for GLS, LVEF in 2D and end-diastolic and end-systolic volumes.

Statistical analyses

Data are expressed as means ± standard deviations, medians (interquartile ranges) or absolute numbers and frequencies. All strain values between the two platforms were compared using the *t* test for paired observations. Agreement between ultrasound systems and software packages was tested using Bland-Altman analysis [20], including the calculation of bias and limits of agreement. Intra- and interobserver variabilities were evaluated using the concordance correlation coefficient (CCC) ± standard error.

A P value ≤ 0.05 was considered significant. All statistical analyses were performed using STATA V12 statistical software (StataCorp, College Station, TX, USA).

Results

Study population

Ninety-one patients were included prospectively from February to June 2015. Eleven patients were excluded from this analysis because of poor quality imaging (more than one segment not visualized correctly). Eight patients (8.8%) were excluded because of poor visualization of the apical four-chamber view segment, and three patients (3.2%) were excluded for poor echogenicity in the apical two-chamber view. Data from 80 patients were analysed for multilayer measurement of GLS.

Table 1 summarizes the patients' baseline characteristics. The mean age was 55.3 ± 16.3 years and 61% were women. Hypertension and dyslipidaemia were found in 25 and 20% of the population, respectively. Eighty-one percent of patients were in New York Heart Association class I; 17.5% were in class II. Haematological cancer (31.3%) and lung cancer (22.5%) were the most common neoplasias.

The main 2D echocardiographic results are depicted in Table 1. Mean LVEF was 62.2% (57.2 to 66.1%) when measured with the Siemens platform and 62.3% (57.3 to 65%) with the GE platform, with a CCC of 0.956 ± 0.010 for comparison of the two platforms.

Table 1 Baseline patient characteristics (n = 80).

Variable	Value
Demographic data	
Age (years)	55.3 ± 16.3
Men	31 (38.8)
Cardiovascular risk factors	
Diabetes mellitus	5 (6.3)
Dyslipidaemia	16 (20.0)
Hypertension	20 (25.0)
History of ACS, CABG	1 (1.3)
Tobacco use	33 (41.3)
Clinical status	
NYHA class	
I	65 (81.3)
II	14 (17.5)
III	1 (1.3)
IV	0
Systolic blood pressure (mmHg)	125 (112 to 135)
Diastolic blood pressure (mmHg)	68 (58 to 76)
Heart rate	72 (64 to 84)
Treatment	
Angiotensin-converting enzyme inhibitor	8 (10.0)
Angiotensin receptor blocker	6 (7.5)
Beta-blocker	10 (12.5)
Diuretic	0
Antialdosterone	1 (1.3)
Echocardiographic data	
LV end-diastolic dimension (mm/m^2)	25.6 (23.8 to 28.1)
LV end-systolic dimension (mm/m^2)	17.2 (15.2 to 18.9)
E/A	0.94 (0.73 to 1.17)
E/e' mean	7.05 (5.88 to 8.21)

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). ACS: acute coronary syndrome; CABG: coronary artery bypass graft; LV: left ventricular; NYHA: New York Heart Association.

Intervendor comparison

Analysis of GLS according to myocardial layer and vendor

GLS values according to layer, chamber view and platform are presented in Table 2, for apical four-, two- and three-chamber views, respectively.

For a given platform, GLS values decreased from the endocardial layer to the epicardial layer. For a given view, GLS values obtained for each layer with the Siemens platform were systematically lower than those obtained with the GE platform (P < 0.0001 for all comparisons). Poor agreement was observed between the two platforms, irrespective of the view or the layer (CCCs < 0.4 for all comparisons) (Figs. 3—8 and A1—3).

A more important bias was found for the epicardial layer compared with the mid-myocardial layer and the

Table 2 Global longitudinal strain according to layer, chamber view and platform.

	GLS values		*P*	Bias (95% LOA)	CCC ± SE
	GE platform	Siemens platform			
End GLS 4ch	20.7 (18.5 to 23.5)	18.8 (17.1 to 21.0)	< 0.0001	1.879 (−5.598 to 9.355)	0.315 ± 0.089
Mid GLS 4ch	18.2 (16.1 to 20.5)	15.5 (13.6 to 17.2)	< 0.0001	2.625 (−3.931 to 9.181)	0.222 ± 0.075
Epi GLS 4ch	15.9 (14.1 to 17.9)	11.8 (10.6 to 14.2)	< 0.0001	3.860 (2.533 to 10.252)	0.125 ± 0.055
End GLS 2ch	21.7 (19.0 to 24.1)	18.0 (16.7 to 20.9)	< 0.0001	3.220 (−4.367 to 10.808)	0.234 ± 0.075
Mid GLS 2ch	19.3 (17.0 to 21.8)	15.3 (13.2 to 17.1)	< 0.0001	4.054 (−2.445 to 10.553)	0.180 ± 0.057
Epi GLS 2ch	17.3 (15.1 to 19.4)	12.0 (10.3 to 14.0)	< 0.0001	5.312 (−1.245 to 11.868)	0.042 ± 0.040
End GLS 3ch	22.2 (19.8 to 25.7)	18.5 (16.6 to 21.4)	< 0.0001	3.293 (−5.106 to 11.693)	0.310 ± 0.078
Mid GLS 3ch	19.2 (17.3 to 22.3)	15.1 (13.6 to 17.5)	< 0.0001	4.055 (−2.394 to 10.503)	0.291 ± 0.061
Epi GLS 3ch	16.9 (15.2 to 14.2)	12.0 (9.6 to 13.5)	< 0.0001	5.244 (−0.638 to 11.125)	0.189 ± 0.045

GLS data are expressed as median (interquartile range). 2ch: in apical two-chamber view; 3ch: in apical three-chamber view; 4ch: in apical four-chamber view; CCC: concordance correlation coefficient; End: endocardial layer; Epi: epicardial layer; GE: General Electric; GLS: global longitudinal strain; LOA: limits of agreement; Mid; mid-myocardial layer; SE: standard error.

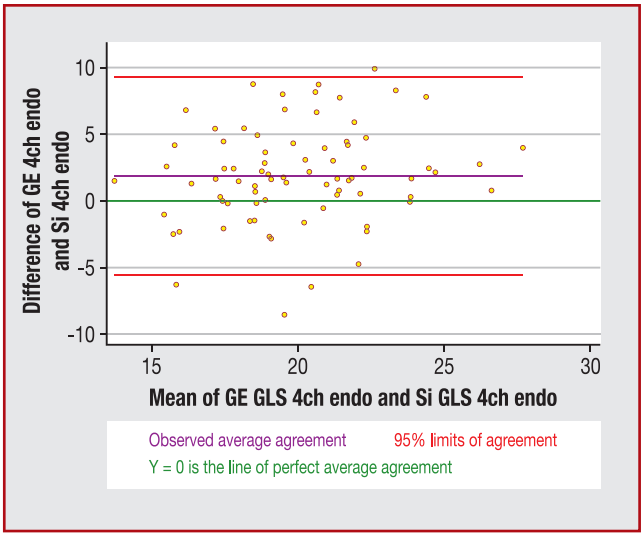

Figure 3. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for endocardial GLS in four-chamber view (GLS 4ch endo). Bias (95% limits of agreement) = 1.879 (−5.598 to 9.355).

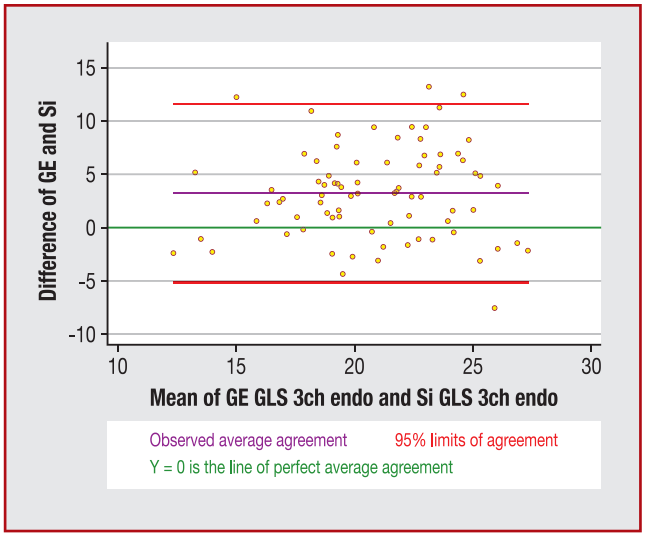

Figure 4. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for endocardial GLS in three-chamber view (GLS 3ch endo). Bias (95% limits of agreement) = 3.293 (−5.106 to 11.693).

endocardial layer, irrespective of the view considered ($P < 0.0001$ for all comparisons).

Comparison of average GLS values according to view and platform

Average GLS values for each view are given in Table 3. The average GLS values for the four-, two- and three-chamber views were significantly higher with the GE platform ($P < 0.0001$). There was poor agreement between the two platforms, with CCCs ranging from 0.172 to 0.274 for all comparisons.

Comparison of interlayer gradient of GLS value according to platform

Comparisons of interlayer gradients of GLS value according to chamber view and platform are detailed in Table 4.

In the apical four-chamber view, the interlayer gradient was significantly higher for the Siemens platform compared with the GE platform, as well as in the apical two- and three-chamber views ($P < 0.0001$ for all comparisons).

Low agreement was observed between the two vendors, regardless of the interlayer gradient and apical view considered ($P < 0.0001$ for all comparisons), with CCCs ranging from −0.042 to 0.135.

Observer variability for GLS

Intraobserver variability using the GE software was good, with CCCs varying from 0.732 ± 0.100 to 0.903 ± 0.043 (Table A.1). Intraobserver variability using the Siemens software was also good, with CCCs varying from 0.882 ± 0.052 to 0.960 ± 0.018 (Table A.2).

Table 3 Values of global longitudinal strain according to average global longitudinal strain and platform.

	GLS value		*P*	Bias (95% LOA)	CCC ± SE
	GE platform	Siemens platform			
Av GLS 4ch	18.3 (16.1 to 20.6)	15.3 (13.7 to 17.3)	< 0.0001	2.788 (−3.744 to 9.319)	0.224 ± 0.073
Av GLS 2ch	19.4 (17.5 to 22.5)	15.1 (13.7 to 17.4)	< 0.0001	4.195 (−2.313 to 10.704)	0.172 ± 0.055
Av GLS 3ch	19.5 (17.1 to 21.8)	15.4 (13.3 to 16.9)	< 0.0001	4.197 (−2.375 to 10.769)	0.274 ± 0.060

GLS data are expressed as median (interquartile range). 2ch: in apical two-chamber view; 3ch: in apical three-chamber view; 4ch: in apical four-chamber view; Av: average; CCC: concordance correlation coefficient; GE: General Electric; GLS: global longitudinal strain; LOA: limits of agreement; SE: standard error.

Table 4 Values of global longitudinal strain according to interlayer gradient using the two platforms.

	GLS value		*P*	Bias (95% LOA)	CCC ± SE
	GE platform	Siemens platform			
End-epi gr GLS 4ch	4.5 (3.6 to 5.2)	7.1 (5.7 to 8.2)	< 0.0001	−2.377 (−7.185 to −2.430)	0.091 ± 0.050
End-mid gr GLS 4ch	2.6 (2.1 to 3.1)	3.4 (2.7 to 4.0)	< 0.0001	−0.746 (−3.404 to 1.912)	0.135 ± 0.071
Mid-epi gr GLS 4ch	2.1 (1.8 to 2.7)	3.4 (2.8 to 4.2)	< 0.0001	−1.235 (−3.542 to 1.072)	0.111 ± 0.052
End-epi gr GLS 2ch	4.5 (3.6 to 5.2)	6.5 (5.0 to 8.0)	< 0.0001	2.104 (−7.583 to 3.375)	−0.011 ± 0.055
End-mid gr GLS 2ch	2.4 (1.9 to 2.9)	3.3 (2.4 to 4.0)	< 0.0001	−0.834 (−3.836 to 2.169)	−0.042 ± 0.065
Mid-epi gr GLS 2ch	2.1 (1.6 to 2.4)	3.1 (2.5 to 4.1)	< 0.0001	−1.250 (−3.951 to 1.451)	0.008 ± 0.046
End-epi gr GLS 3ch	5.4 (4.6 to 6.6)	7.5 (5.6 to 7.5)	< 0.0001	−1.950 (−7.761to 3.860)	0.034 ± 0.068
End-mid gr GLS 3ch	2.9 (2.5 to 3.6)	3.7 (2.7 to 4.8)	0.0001	−0.761 (−3.983 to 2.461)	0.014 ± 0.079
Mid-epi gr GLS 3ch	2.5 (2.1 to 3.0)	3.6 (2.8 to 4.6)	< 0.0001	−1.189 (−3.899 to 1.520)	0.046 ± 0.056

GLS data are expressed as median (interquartile range). 2ch: in apical two-chamber view; 3ch: in apical three-chamber view; 4ch: in apical four-chamber view; CCC: concordance correlation coefficient; end-epi gr GLS: interlayer gradient of GLS between endocardial and epicardial layers; end-mid gr GLS: interlayer gradient of GLS between endocardial and mid-myocardial layers; GE: General Electric; GLS: global longitudinal strain; LOA: limits of agreement; Mid-epi gr GLS: interlayer gradient of GLS between mid-myocardial and epicardial layers; SE: standard error.

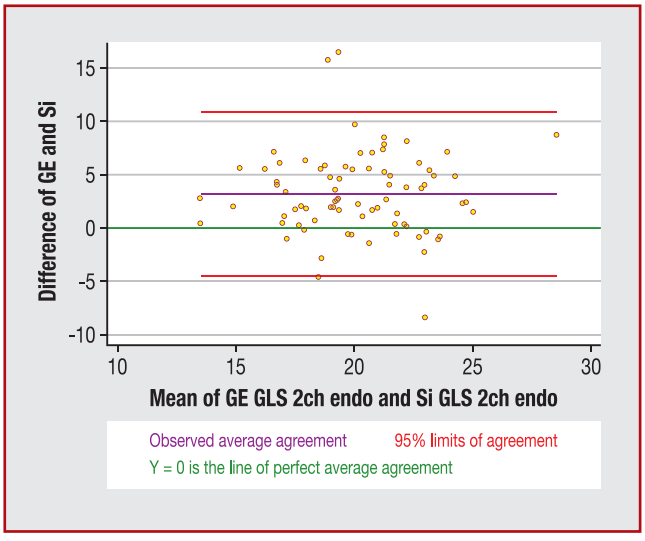

Figure 5. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for endocardial GLS in two-chamber view (GLS 2ch endo). Bias (95% limits of agreement) = 3.220 (−4.367 to 10.808).

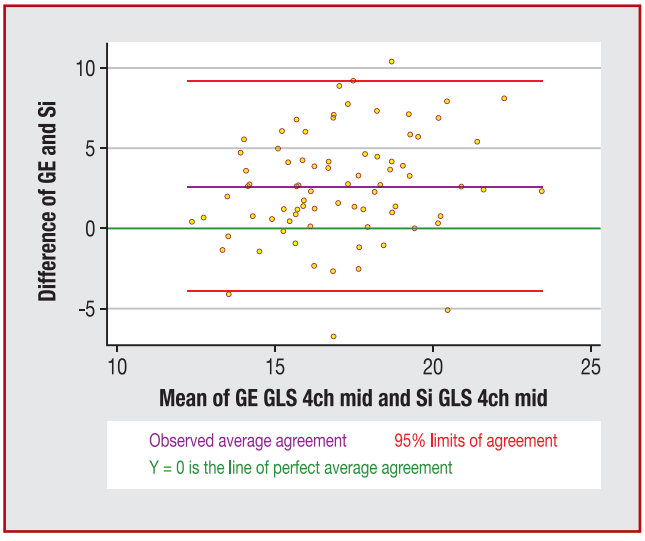

Figure 6. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for mid-myocardial GLS in four-chamber view (GLS 4ch mid). Bias (95% limits of agreement) = 2.625 (−3.931 to 9.181).

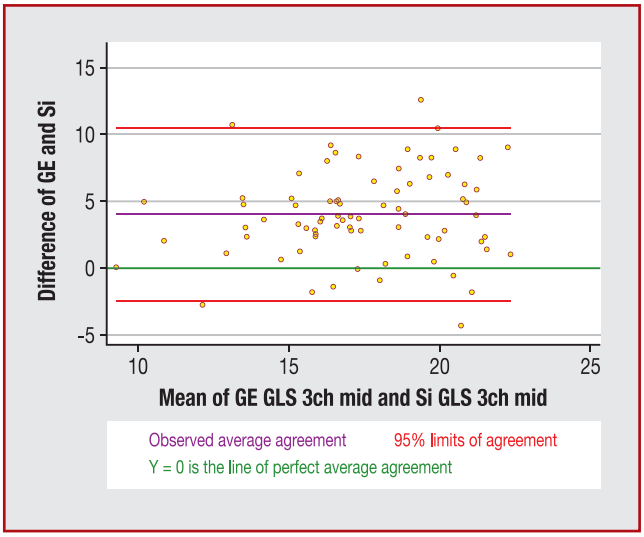

Figure 7. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for mid-myocardial GLS in three-chamber view (GLS 3ch mid). Bias (95% limits of agreement) = 4.055 2.394 to 10.503).

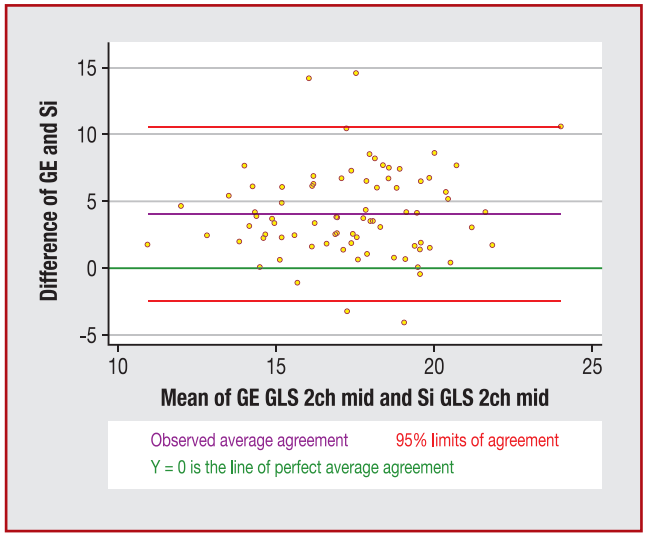

Figure 8. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for mid-myocardial GLS in two-chamber view (GLS 2ch mid). Bias (95% limits of agreement) = 4.054 (—2.445 to 10.553).

There was good agreement between observers concerning interobserver reproducibility using the GE software, with CCCs varying from 0.818 ± 0.077 to 0.924 ± 0.033 (Table A.3), and using the Siemens software, with CCCs varying from 0.872 ± 0.054 to 0.969 ± 0.013 (Table A.4).

Observer variability for 2D measurements for the Siemens platform

Variability was found to be acceptable, with a CCC value of 0.310 ± 0.299 for 2D interobserver variability, and 0.710 ± 0.175 for 2D intraobserver variability.

Observer variability for 2D measurements for the GE platform

Variability was acceptable, with a CCC value of 0.439 ± 0.280 for 2D interobserver variability; CCC 0.419 ± 0.217 for 2D intraobserver variability.

Discussion

Our study aimed to compare two ultrasound manufacturers and their specific software for multilayer GLS analysis. We intended to limit already known factors of variability that affect monolayer GLS measurement and could potentially affect multilayer GLS measurement.

We found that assessment of multilayer strain using either platform presented a transmural gradient of strain, with a decrease in the value of GLS from the endocardial to the epicardial layer. However, our results demonstrated poor agreement between the two platforms and their software for evaluation of layer-specific GLS. We observed a systematic bias, regardless of the considered layers, views or interlayer gradients.

Factors of variability in transmural GLS measured using speckle tracking

Normal values of GLS can be influenced by several factors, such as anthropometric criteria, haemodynamic variables, vendor characteristics and software variables [4,9,11,21,22]. Age has been reported to influence GLS value; Sun et al. observed that GLS values in healthy adults declined with age [22]. Sex also plays a role and may influence the normal value of GLS [9,21,23,24]; Kocabay et al. found in 247 healthy adults that longitudinal strain was significantly higher in women [24]. Blood pressure is an important variable that may influence GLS; a meta-analysis including 2597 patients demonstrated a correlation between strain value and blood pressure level [11].

Intervendor variability using monolayer strain has been explored in several studies, demonstrating discordant results. Takigiku et al. [6] performed a prospective study in 817 healthy adults, which sought to determine normal values of monolayer strain. Three platforms were compared in a sample of the population. The authors found that normal GLS values varied according to sex, age and vendor [6].

These discrepancies led to a consensus between manufacturers and physicians to standardize strain measurement using speckle tracking [12]. Yang et al. demonstrated better intervendor agreement for GLS after a standardization initiative comparing two manufacturers (GE [VIVID E9] and Philips [IE33; Amsterdam, the Netherlands]) and their dedicated software [25].

Reproducibility of multilayer strain

Efforts have been made to improve the intervendor reproducibility of transmural layer strain, with a consensus on the definition of transmural layer strain between clinicians and industry [12]. Nevertheless, this approach has not yet been performed for multilayer strain. We investigated variability in multilayer strain in patients receiving oral molecular

targeted agents. Observations with the two platforms were in line with previous reports showing a transmural gradient of GLS, with decreasing values from the endocardial layer to the epicardial layer. Shi et al. found a transmural gradient of strain, with decreasing values from the endocardial to the epicardial layer, and that sex, height and cardiac frequency were predictors of GLS value [17]. This result was shown previously in a study by Adamu et al., which aimed to determine myocardial deformation for the three-myocardial layers in normal subjects and to define the effect of regional ischaemic LV dysfunction on deformation of each of the three layers [13].

Nevertheless, we found poor concordance between the two platforms when assessing multilayer measurement. Although we intended to reduce established variability factors for monolayer strain values using a strict protocol, we found poor agreement between the GE and Siemens platforms for multilayer measurement of GLS, whatever the layer, gradient or chamber view considered.

Several hypotheses can be proposed to explain the poor reproducibility of multilayer strain. Sources of intervendor variability depend on image quality, which may vary among patients, echocardiographers and machines. Furthermore, image characteristics are not the same among ultrasound machines because of differences in spatial and temporal resolution, filter settings and other post-processing effects [26]. It is unknown to what extent such differences could account for the variability in estimates of multilayer strain. Measured values depend directly on the physical definition of a variable. Software packages may use different algorithms for measurement of deformation, regularization of data and presentation of results. Moreover, user interaction and (semi)automatic user guidance may have a substantial effect on measurement variability [7]. Because post-processing algorithms are proprietary, and are not usually disclosed, their effect can be assessed only by comparing results. In the literature, there are several definitions of the mid-myocardial layer, which could be a cause of variability among different manufacturers. In our study, the mid layer was defined for both GE and Siemens as the average of the endocardial and epicardial layers.

We found good intra- and interobserver variability. In line with our results, Coiro et al. showed mean relative intraobserver and interobserver differences of $<5\%$ and $<7.5\%$, respectively, for strain multilayer assessment from a cohort of 50 patients [18]. A study from Ozawa et al. also found good reproducibility, with interobserver correlation coefficients in transmural, endocardial and epicardial GLS of 0.81, 0.83 and 0.80, respectively, and intraobserver correlation coefficients in transmural, endocardial and epicardial GLS of 0.97, 0.97 and 0.94, respectively [27]. However, as mentioned above, these results are data from strain multilayer using two layers (endocardial and epicardial).

Clinical implications for patients undergoing chemotherapy

Recent guidelines have recommended the use of GLS for the early detection of myocardial injury in patients receiving cardiotoxic chemotherapy [1].

Several studies have been published with the aim of assessing GLS in different clinical cases, especially in myocardial ischaemia. Thus, we estimated that it is important to highlight that this technique seems to present the same limitations as monolayer strain and efforts to reduce intervendor variability will also be needed. In accordance with standardization of monolayer strain, a consensus between clinicians and manufacturers should be reached to standardize the assessment of multilayer strain.

Study limitations

The population included was small and we assessed only two manufacturers. We did not assess global radial strain and global circumferential strain because, in the literature, these variables show more variability than GLS, which is the most sensitive and robust technique for early identification of myocardial disease [3,4]. Furthermore, GLS is the criterion recommended in the guidelines for patients undergoing chemotherapy [1].

Several companies have developed software that provides measures of curves of strain from different myocardial ''layers''; however, it has not been carefully documented that different instruments (in fact, any of the instruments) can resolve the three separate LV myocardial layers in an unambiguous manner when one considers the spatial resolution, size of the region of interest, displacement of the ventricular walls during the cardiac and respiratory cycles and the thickness of the myocardial walls.

Conclusions

Comparison of layer-specific GLS values from two platforms with their proprietary software revealed poor concordance, with systematically lower values for Siemens compared with GE software. Both platforms demonstrated a transmural gradient of GLS, with a decrease in value from the endocardial to the epicardial layer. Intra- and interobserver variabilities were satisfactory.

Evaluation of myocardial deformation using layer-specific strain still presents the same limitation as single-layer strain assessment, showing that this tool may require standardization between manufacturers. Further studies are needed to compare other ultrasound systems and their software packages.

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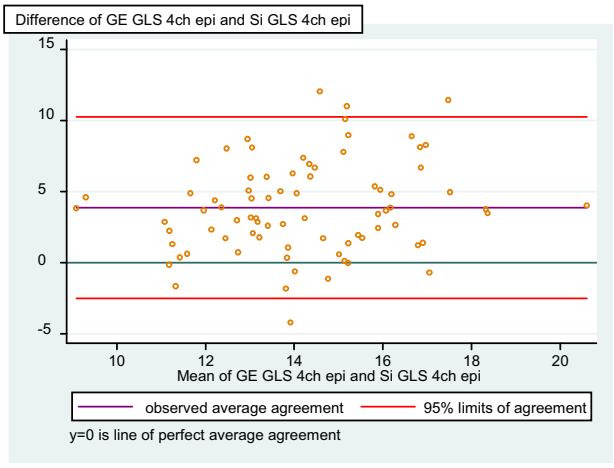
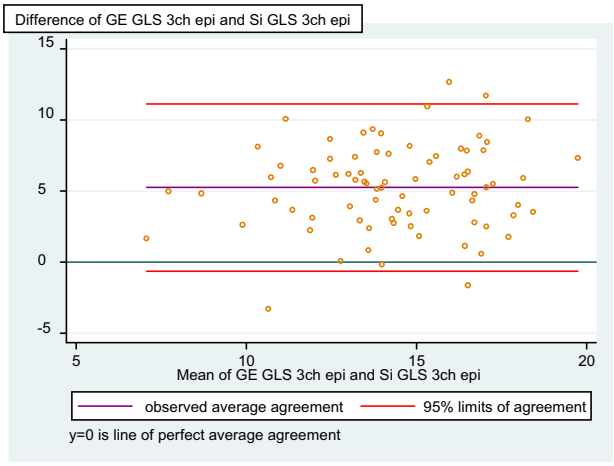
The other authors declare that they have no competing interest.

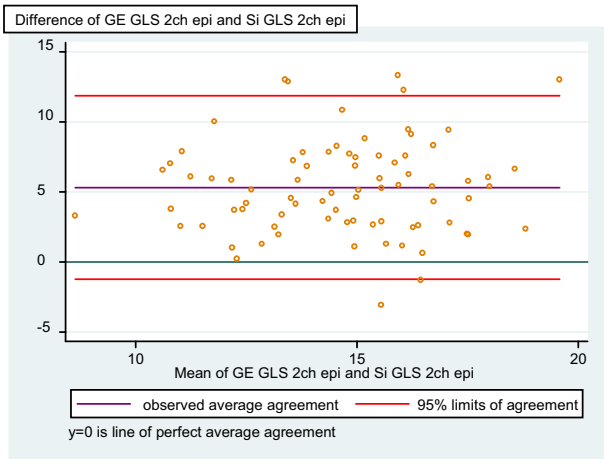
Appendix 1. Figure A.1. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for epicardial GLS in four-chamber view (GLS 4ch epi). Bias (95% limits of agreement) = 3.860 (−2.533 to 10.252).



Appendix 2. Figure A.2. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for epicardial GLS in three-chamber view (GLS 3ch epi). Bias (95% limits of agreement) = 5.244 (−0.638 to 11.125).



Appendix 3. Figure A.3. Bland-Altman plot of difference in multilayer global longitudinal strain (GLS) between General Electric (GE) and Siemens (Si) platforms for epicardial GLS in two-chamber view (GLS 2ch epi). Bias (95% limits of agreement) = 5.312 (−1.245 to 11.868).



Appendix 4. Table A.1 Intraobserver variability of global longitudinal strain according to layer, using General Electric software (*n* = 20).

	Bias (95% LOA)	CCC ± SE
End GLS 4ch	−0.255 (−3.205 to 2.695)	0.887 ± 0.049
Mid GLS 4ch	−0.425 (−2.730 to 1.880)	0.903 ± 0.043
Epi GLS 4ch	−0.500 (−3.284 to 2.289)	0.840 ± 0.067
End GLS 2ch	0.040 (−3.359 to 3.439)	0.795 ± 0.087
Mid GLS 2ch	−0.005 (−3.263 to 3.253)	0.761 ± 0.095
Epi GLS 2ch	−0.180 (−3.500 to 3.140)	0.732 ± 0.100
End GLS 3ch	−0.160 (−3.513 to 3.193)	0.857 ± 0.063
Mid GLS 3ch	−0.185 (−3.270 to 2.900)	0.854 ± 0.064
Epi GLS 3ch	−0.170 (−3.277 to 2.937)	0.836 ± 0.070

2ch: in apical two-chamber view; 3ch: in apical three-chamber view; 4ch: in apical four-chamber view; CCC: concordance correlation coefficient; End: endocardial layer; Epi: epicardial layer; GLS: global longitudinal strain; LOA: limits of agreement; Mid: mid-myocardial layer; SE: standard error.

Appendix 5. Table A.2 Intraobserver variability of global longitudinal strain according to layer, using Siemens software (*n* = 20).

	Bias (95% LOA)	CCC ± SE
End GLS 4ch	−0.062 (−2.135 to 2.010)	0.906 ± 0.039
Mid GLS 4ch	0.006 (−1.855 to 1.867)	0.882 ± 0.052
Epi GLS 4ch	−0.064 (−1.447 to 1.318)	0.923 ± 0.033
End GLS 2ch	0.670 (−1.302 to 2.643)	0.924 ± 0.033
Mid GLS 2ch	0.021 (−2.124 to 2.165)	0.937 ± 0.028
Epi GLS 2ch	−0.029 (−2.206 to 2.148)	0.930 ± 0.032
End GLS 3ch	−0.440 (−2.181 to 1.302)	0.960 ± 0.018
Mid GLS 3ch	−0.266 (−2.074 to 1.541)	0.951 ± 0.022
Epi GLS 3ch	−0.166 (−2.196 to 1.864)	0.925 ± 0.033

2ch: in apical two-chamber view; 3ch: in apical three-chamber view; 4ch: in apical four-chamber view; CCC: concordance correlation coefficient; End: endocardial layer; Epi: epicardial layer; GLS: global longitudinal strain; LOA: limits of agreement; Mid: mid-myocardial layer; SE: standard error.

Appendix 6. Table A.3 Interobserver variability of global longitudinal strain according to layer, using General Electric software (*n* = 20).

	Bias (95% LOA)	CCC ± SE
End GLS 4ch	−0.350 (−2.933 to 2.233)	0.910 ± 0.040
Mid GLS 4ch	−0.530 (−2.968 to 1.908)	0.883 ± 0.051
Epi GLS 4ch	−0.020 (−2.527 to 2.487)	0.891 ± 0.049
End GLS 2ch	0.000 (−2.453 to 2.453)	0.907 ± 0.040
Mid GLS 2ch	0.100 (−2.017 to 2.217)	0.924 ± 0.033
Epi GLS 2ch	−0.300 (−2.725 to 2.125)	0.890 ± 0.048
End GLS 3ch	−0.485 (−3.900 to 2.930)	0.846 ± 0.066
Mid GLS 3ch	−0.515 (−3.793 to 2.763)	0.818 ± 0.077
Epi GLS 3ch	−0.175 (−3.316 to 2.966)	0.829 ± 0.073

2ch: in apical two-chamber view; 3ch: in apical three-chamber view; 4ch: in apical four-chamber view; CCC: concordance correlation coefficient; End: endocardial layer; Epi: epicardial layer; GLS: global longitudinal strain; LOA: limits of agreement; Mid: mid-myocardial layer; SE: standard error

Appendix 7. Table A.4 Interobserver variability of global longitudinal strain according to layer, using Siemens software (*n* = 20).

	Bias (95% LOA)	CCC ± SE
End GLS 4ch	−0.479 (−1.341 to 0.383)	0.969 ± 0.013
Mid GLS 4ch	−0.405 (−2.220 to 1.410)	0.872 ± 0.054
Epi GLS 4ch	0.091 (−0.1.305 to 1.486)	0.920 ± 0.035
End GLS 2ch	−0.773 (−2.614 to 1.068)	0.923 ± 0.033
Mid GLS 2ch	−0.056 (−2.221 to 2.108)	0.936 ± 0.029
Epi GLS 2ch	−0.029 (−2.097 to 2.040)	0.935 ± 0.029
End GLS 3ch	0.412 (−1.338 to 2.163)	0.961 ± 0.017
Mid GLS 3ch	0.254 (−1.574 to 2.082)	0.950 ± 0.023
Epi GLS 3ch	0.140 (−1.986 to 2.176)	0.925 ± 0.033

2ch: in apical two-chamber view; 3ch: in apical three-chamber view; 4ch: in apical four-chamber view; CCC: concordance correlation coefficient; End: endocardial layer; Epi: epicardial layer; GLS: global longitudinal strain; LOA: limits of agreement; Mid: mid-myocardial layer; SE: standard error.

References

[1] Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2014;15:1063—93.

[2] Rhea IB, Uppuluri S, Sawada S, Schneider BP, Feigenbaum H. Incremental prognostic value of echocardiographic strain and its association with mortality in cancer patients. J Am Soc Echocardiogr 2015;28:667—73.

[3] Koopman LP, Slorach C, Manlhiot C, et al. Assessment of myocardial deformation in children using Digital Imaging and Communications in Medicine (DICOM) data and vendor independent speckle tracking software. J Am Soc Echocardiogr 2011;24:37—44.

[4] Manovel A, Dawson D, Smith B, Nihoyannopoulos P. Assessment of left ventricular function by different speckle-tracking software. Eur J Echocardiogr 2010;11:417—21.

[5] Risum N, Ali S, Olsen NT, 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—203.

[6] Takigiku K, Takeuchi M, Izumi C, et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. Circ J 2012;76:2623—32.

[7] Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: the EACVI/ASE intervendor comparison study. J Am Soc Echocardiogr 2015;28:1171—81 [e2].

[8] Imbalzano E, Zito C, Carerj S, et al. Left ventricular function in hypertension: new insight by speckle tracking echocardiography. Echocardiography 2011;28:649—57.

[9] Marwick TH, Leano RL, Brown J, et al. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography: definition of normal range. JACC Cardiovasc Imaging 2009;2:80—4.

[10] Reckefuss N, Butz T, Horstkotte D, Faber L. Evaluation of longitudinal and radial left ventricular function by two-dimensional speckle-tracking echocardiography in a large cohort of normal probands. Int J Cardiovasc Imaging 2011;27:515—26.

[11] Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 2013;26:185—91.

[12] Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr 2015;28:183—93.

[13] Adamu U, Schmitz F, Becker M, Kelm M, Hoffmann R. Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters. Eur J Echocardiogr 2009;10:303—8.

[14] Leitman M, Lysiansky M, Lysyansky P, 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.

[15] Sarvari SI, Haugaa KH, Zahid W, et al. Layer-specific quantification of myocardial deformation by strain echocardiography may reveal significant CAD in patients with non-ST-segment elevation acute coronary syndrome. JACC Cardiovasc Imaging 2013;6:535—44.

[16] Ejlersen JA, Poulsen SH, Mortensen J, May O. Diagnostic value of layer-specific global longitudinal strain during adenosine stress in patients suspected of coronary artery disease. Int J Cardiovasc Imaging 2017;33:473—80.

[17] Shi J, Pan C, Kong D, Cheng L, Shu X. Left ventricular longitudinal and circumferential layer-specific myocardial strains and their determinants in healthy subjects. Echocardiography 2016;33:510—8.

[18] Coiro S, Huttin O, Bozec E, et al. Reproducibility of echocardiographic assessment of 2D-derived longitudinal strain parameters in a population-based study (the STANISLAS Cohort study). Int J Cardiovasc Imaging 2017;33:1361—9.

[19] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233—70.

[20] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307—10.

[21] Dalen H, Thorstensen A, Aase SA, et al. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the HUNT study in Norway. Eur J Echocardiogr 2010;11:176—83.

[22] Sun JP, Lee AP, Wu C, et al. Quantification of left ventricular regional myocardial function using two-dimensional speckle tracking echocardiography in healthy volunteers — a multicenter study. Int J Cardiol 2013;167:495—501.

[23] Hurlburt HM, Aurigemma GP, Hill JC, et al. Direct ultrasound measurement of longitudinal, circumferential, and radial strain using 2-dimensional strain imaging in normal adults. Echocardiography 2007;24:723—31.

[24] Kocabay G, Muraru D, Peluso D, et al. Normal left ventricular mechanics by two-dimensional speckle-tracking echocardiography. Reference values in healthy adults. Rev Esp Cardiol (Engl Ed) 2014;67:651—8.

[25] Yang H, Marwick TH, Fukuda N, et al. Improvement in strain concordance between two major vendors after the strain standardization initiative. J Am Soc Echocardiogr 2015;28:642—8 [e7].

[26] Negishi K, Lucas S, Negishi T, Hamilton J, Marwick TH. What is the primary source of discordance in strain measurement between vendors: imaging or analysis? Ultrasound Med Biol 2013;39:714—20.

[27] Ozawa K, Funabashi N, Kamata T, Kobayashi Y. Inter- and intraobserver consistency in LV myocardial strain measurement using a novel multilayer technique in patients with severe aortic stenosis and preserved LV ejection fraction. Int J Cardiol 2017;228:687—93.