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REVIEW

Myocardial strain imaging: review of general principles, validation, and sources of discrepancies

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Myocardial tissue tracking imaging techniques have been developed for a more accurate evaluation of myocardial deformation (i.e. strain), with the potential to overcome the limitations of ejection fraction (EF) and to contribute, incremental to EF, to the diagnosis and prognosis in cardiac diseases. While most of the deformation imaging techniques are based on the similar principles of detecting and tracking specific patterns within an image, there are intra- and inter-imaging modality inconsistencies limiting the wide clinical applicability of strain. In this review, we aimed to describe the particularities of the echocardiographic and cardiac magnetic resonance deformation techniques, in order to understand the discrepancies in strain measurement, focusing on the potential sources of variation: related to the software used to analyse the data, to the different physics of image acquisition and the different principles of 2D vs. 3D approaches. As strain measurements are not interchangeable, it is highly desirable to work with validated strain assessment tools, in order to derive information from evidence-based data. There is, however, a lack of solid validation of the current tissue tracking techniques, as only a few of the commercial deformation imaging softwares have been properly investigated. We have, therefore, addressed in this review the neglected issue of suboptimal validation of tissue tracking techniques, in order to advocate for this matter.

Keywords strain • speckle tracking imaging • feature tracking • tagging • echocardiography • cMR • review

Introduction

Assessment of cardiac contractile function remains a challenge in current cardiology. Indeed, ejection fraction (EF), the traditional parameter used to describe left ventricular (LV) function, presents significant limitations,[1] related to its volumetric nature, suboptimal reproducibility, and inability to reflect regional LV function. This has prompted for a more in-depth characterization of LV mechanics through non-invasive evaluation of myocardial deformation, i.e. strain. Strain[2] is the deformation produced by the application of a force; myocardial strain represents percent change in myocardial length from relaxed to contractile state. Unlike EF, strain allows studying the different spatial components of contractile function in either longitudinal strain (LS), circumferential strain (CS), or radial strain (RS) directions, both globally and regionally. However, similar to EF, strain represents a load-dependent estimation of cardiac function and neither is able to depict the true myocardial contractility.

Assessment of LV deformation through quantification of strain has witnessed considerable development, from echocardiographic determined velocity of circumferential fibre shortening,[3] cardiac magnetic resonance (cMR) tissue tagging,[4] tissue Doppler echocardiography[5–8] to current speckle tracking echocardiography (STE), and feature tracking (FT) approaches.[9–12] Alterations of strain were found to occur in the setting of maintained EF[13,14] and were reported to provide additional prognostic value over EF alone in a multitude of clinical scenarios, ranging from asymptomatic adults without a previous history of cardiac pathology (as participants of MESA and Framingham studies)[15,16] to valvular heart disease (in particular aortic stenosis[13]) and heart failure with preserved and reduced EF.[17,18] Therefore, deformation imaging techniques have become extremely popular and,

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being applied to numerous research questions, have resulted in an extensive number of published papers, with 'myocardial strain' keyword search hitting nearly 8000 results in PubMed alone. Notwithstanding the enthusiastic scientific interest, myocardial deformation assessment has only partly breached the clinical setting, as several concerns have been raised regarding its robustness in the real-life scenario.

In this review, we attempt to summarize the general principles and technical particularities of current deformation imaging modalities, with particular emphasis on factors explaining differences in measurement values among methods. Further, we aim to provide an overview of current state of validation and intra- and inter-modality comparison.

General principles of deformation imaging techniques

Myocardial deformation can be assessed both from echocardiographic and cMR images, following a similar general workflow, with specific analysis algorithms implemented for each imaging modality. Most deformation imaging techniques share the common principle that specific patterns or features are identified within an image and followed over time in the subsequent images of the sequence by searching the most probable correspondence in successive image frames.[19] Then, local tissue deformation can be estimated by repeating the process for the entire time sequence.

Tissue tracking—general workflow

Typical workflow of tissue tracking is shown in *Figure 1*. Generally, the *initial step* is to recognize the key cardiac events: end-diastole (ED) and end-systole (ES). The *second step* is the definition of a region of interest encompassing the myocardial wall, by semi-automatic contouring of the endocardial and epicardial borders either in ED or in ES or both. *Segmentation* is a critical step as it defines the set of points that will be tracked, introducing variability depending on the user and the segmentation algorithm.[10] Finally, the region of interest is *tracked* throughout the cardiac cycle, and *strain curves* are computed, possibly post-processed. Either the end-systolic or peak systolic strain can be reported.

Technology of tissue tracking—analysis algorithms

Echocardiographic and cMR deformation imaging softwares employ different algorithms to process the image in order to estimate the local myocardial motion. Some techniques exploit specificities of the imaging modality [e.g. cMR tagging], while others are generic and can be applied to any modality (e.g. block-matching techniques for STE and FT). A more detailed technical discussion is included in the Supplementary data online.

Specific modalities of tissue tracking and strain imaging

The tissue tracking strategies can be applied to echocardiographic (2D or 3D), cMR (cine or tagged images), sometimes extending these strategies to account for specificities of the imaging modality (*Figure 2*).The particularities of these techniques to estimate myocardial deformation are discussed below, while advantages and shortcomings of each method are summarized in the following sections.

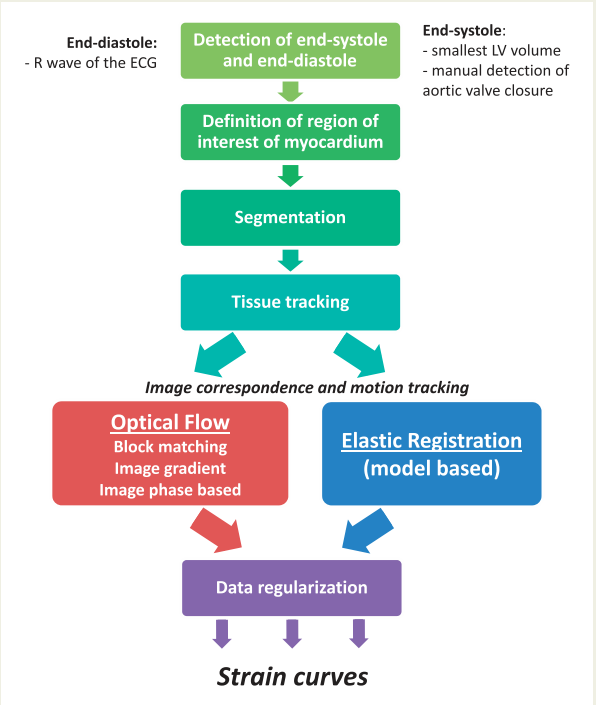

Figure 1 General workflow of strain computation.

cMR tagging

cMR tagging[4] magnetically labels different regions in the myocardium, by creating, prior to image acquisition, locally induced perturbations of the magnetization with selective radiofrequency saturation planes[20] resulting in dark lines. When the saturation pulses are applied in two orthogonal planes, the resulting tagging pattern forms a grid of intrinsic tissue markers known as tags. Because the magnetization is a property of the tissue, the tag lines move along with the tissue in which they are created, deforming during contraction. Tag using harmonic phase imaging (HARP) technique will find the best optical flow for matching the multiple 'channels' of the tagged acquisitions, each tag direction corresponding to one channel. Thus, tracking the tag deformation allows direct evaluation of the myocardial deformation or strain. Variations of tagging for strain computation are Strain Encoding magnetic resonance imaging (SENC)[21] and Displacement Encoding with Stimulated Echos (DENSE).[22] In these techniques, encoding is applied through plane and pixel intensities directly relate to the amount of tissue deformation.

cMR tagging has been widely accepted as the reference standard imaging modality for strain quantification after extensive validation *in vitro*[23] and *in vivo*[24–31] and has allowed the development of the first models of normal and abnormal myocardial motion in humans.[24,29,32–35] The main advantage of tagging is that deformation is directly measured by physical properties of the tissue. Yet, cMR tagging also has certain limitations (*Table 1*). Tagged images have low

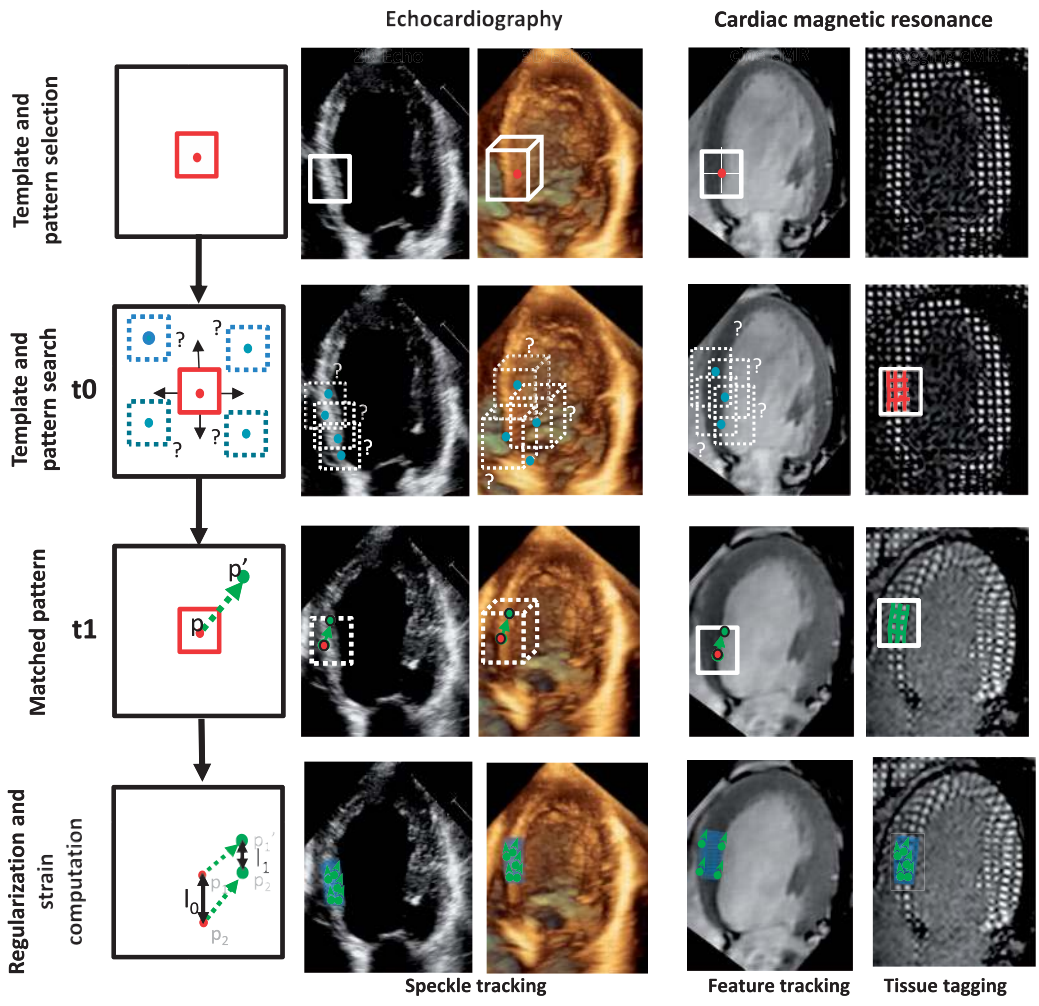

Figure 2 The principles of tissue tracking techniques illustrated on different imaging modalities. The myocardial speckled pattern (on 2D and 3D echocardiography), or anatomical features (on cine-cMR images), or tagging information (on cMR tagging) are identified within an image and followed over time in the subsequent images of the sequence by searching the most probable pattern correspondence.

temporal resolution reaching at the best 20–30 frames/heart-beat. Furthermore, tag deposition in the beginning of systole starts after detection of R wave and introduces a delay of approximately 30 ms. Thus tag deposition may not be exactly at the beginning of cardiac contraction, potentially leading to underestimation of strain, especially at high heart rates. The spatial resolution of tags, as well as the ratio of tag spacing to slice thickness, are also important factors for reliable strain measurements. For this reason, the accuracy of strain estimates from cMR tagging is lower at the endocardial border and in thin-walled regions of the LV, and cMR tagging estimates essentially mid-wall rather than endocardial strain. Finally, tagging requires dedicated acquisition sequence and time-consuming post-processing using specific software solutions such as HARP. Therefore, cMR tagging has mainly remained a research tool and has not undergone as widespread use as more recent methods to measure strain.

Speckle tracking echocardiography

STE is currently the widest available technique to quantify myocardial deformation,[36] mainly because it can be performed on conventional B-Mode images, assuming that image quality is sufficient.

STE analyses LV deformation by tracking cardiac motion from image intensities. Features being tracked can include image contours and image texture, more specifically, the naturally occurring speckled pattern of the myocardium when imaged by ultrasound.[37] For tracking the speckle texture, block-matching method is a commonly used technique. It automatically identifies a pattern within a region or block of interest, compares it to all possible matching regions within the search region and finds the position of the best matching block compared with the original one. STE can be applied to 2D, and more recently to 3D echocardiographic images. Optical flow methods have also been applied to echocardiographic images, as well as elastic

Table 1 Spatial and temporal resolution and strength and weaknesses of different imaging modalities

	2DSTE	3DSTE	cMR-FT	cMR Tagging	cMR SENC	cMR DENSE
Spatial	0.2–0.3 mm	0.4–0.5 mm	1–2 mm in plane 6–10 mm through plane	>1 mm in plane 5–7 mm through plane	1.5–2 mm	1.5–2 mm
Temporal	40–60 frames/s	20–50 frames/s	25–35 phases/heart-beat	20–30 phases/heart-beat	20–30 phases/heart-beat	20–30 phases/heart-beat
Strengths	• Ease and availability • High temporal and spatial resolution	• Good reproducibility of planes • Less foreshortening • Better for CS	• Ease (analysis on standard SSFP cine images) • Reproducibility of planes • Several commercial softwares • Good for LS, CS, and RS	• True tissue markers • Extensive validation • Higher reproducibility of plane acquisitions • 2D and 3D (three strain directions)	• High spatial resolution • Short acquisition time (1 heart-beat) • Fast post-processing • Allows real-time strain for stress cMR	• High spatial resolution • Fast post-processing • Three strain directions form 2D acquisitions
Weaknesses	• Foreshortening • Reproducibility of acquisition planes, particularly for CS and rotation/twist • Through-plane motion • Less performant for CS, RS, and regional strains	• Lower spatial and temporal resolution than 2D STE • Less available than 2D STE • Multibeat acquisition with limited temporal resolution when arrhythmia	• No physical speckles or intramyocardial markers (based on contours only) • Less performant for regional strain • Low spatial and temporal resolution • Less validated • 2D strains only • No rotation/twist	• Requires special sequences and analysis software • Few commercial softwares • Time-consuming acquisition and analysis • Through-plane motion of tags • Tag fading in diastole • Low spatial and temporal resolution • Tag deposition delay may lead to underestimation of strain	• Mainly a research technique • Requires special sequences and analysis software • Not 3D • Low temporal resolution • Measures only through plane strain (CS from long axis, LS from short axis) • No radial strain	• Mainly a research technique • Requires special sequences and analysis software • Low temporal resolution • No true 3D

registration, all of them being able to capture motion and to a certain extent deformation as demonstrated on synthetic images.[38] STE has high spatial and temporal resolution, but depending on the algorithm, typically evaluates speckle motion mainly at endocardial border of the LV, and relatively less in the myocardium.

cMR-FT

cMR-FT is a relatively new 2D imaging technique that can be applied to standard cMR cine SSFP sequences, gaining popularity by allowing measurement of myocardial deformation without the need for dedicated acquisition and complex post-processing.[12,19]

cMR-FT is mainly based on a block-matching approach. It first identifies anatomic features in the cMR image along the myocardial boundaries, defines region of interests around these locations and track them along the cardiac cycle by looking for the most similar region in the next image. Advantages of FT is that strain can be computed on conventional SSFP cine images using several commercial softwares. In contrast to STE and cMR tagging, FT does not seem to distinguish intramyocardial features, as the grey level distribution in cine SSFP images in relatively homogenous. Furthermore, similar to tagging, cine-cMR images have substantially lower spatial and temporal resolution than STE (*Table 1*).

Sources of variations and intra- and inter-modality inconsistencies

The differences in imaging modalities and competitive methodologies result in intra- and inter-modality inconsistencies in deformation estimation as illustrated by *Figure 3A* and *B*. These are explained by several factors, as listed below and summed up in *Table 2*.

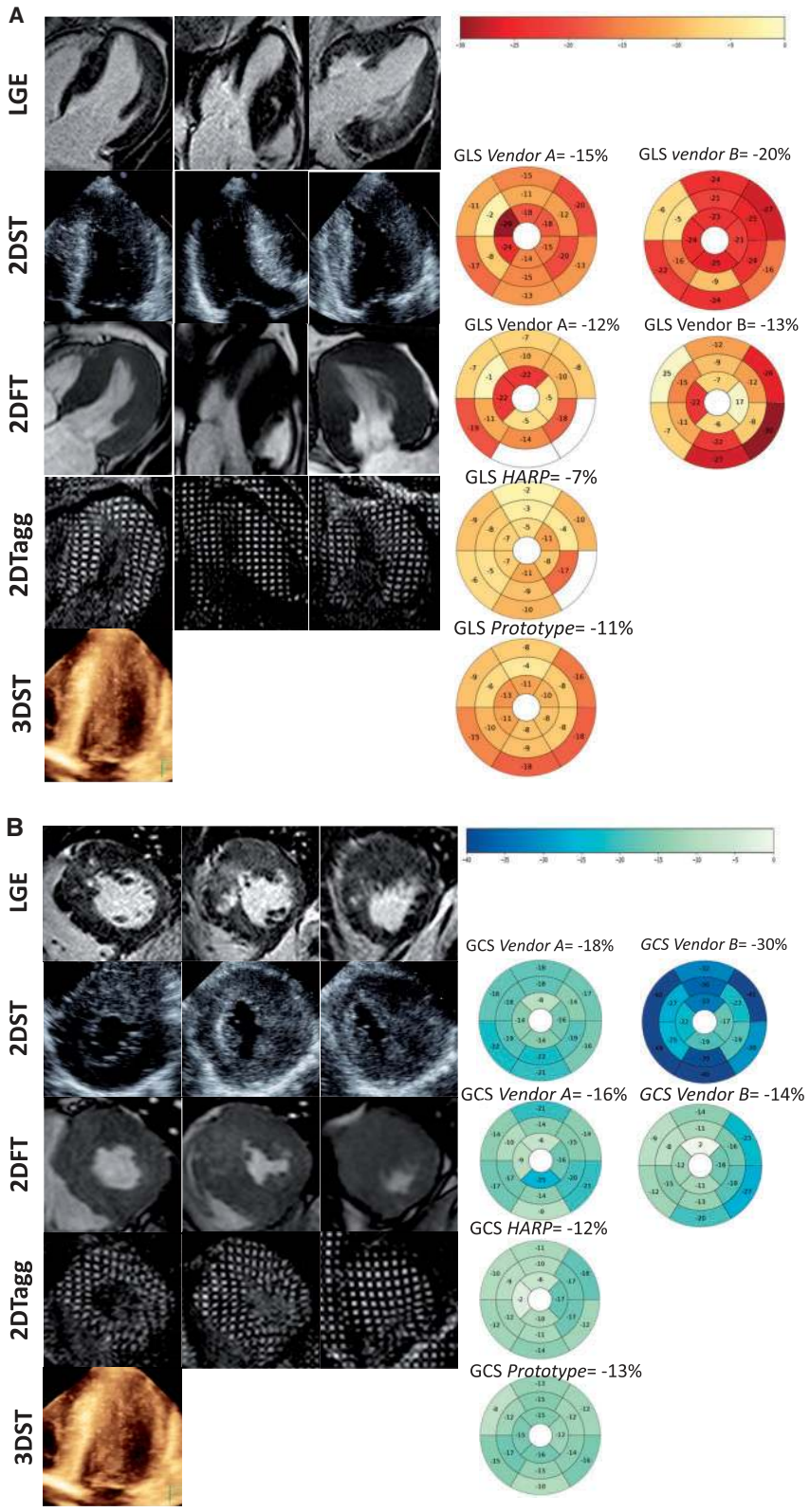

Figure 3 Example of differences in global and regional strain estimates (*A* longitudinal and *B* circumferential) by different modalities and softwares in a patient with hypertrophic cardiomyopathy. Regional strain values are represented in 17 and 18 segment colour-coded bullseyes plots. Excluded segments due to poor image quality or tracking are not colour-coded.

Table 2 Summary of sources of variations and intra- and inter-modality inconsistencies

Imaging modality related factors	Quality of the acquisition process
	Spatial and temporal resolution
	Segmentation misalignment between imaging modalities
Software-related factors	Spatial and temporal smoothing
	Size of the search region
	Favouring tracking in a certain myocardial layer
	Computation of Lagrangian or Eulerian strain
	Calculation of global strain values
	Definition of end-diastole and end-systole
Operator-related factors	Definition of regions of interest
	Experience and training

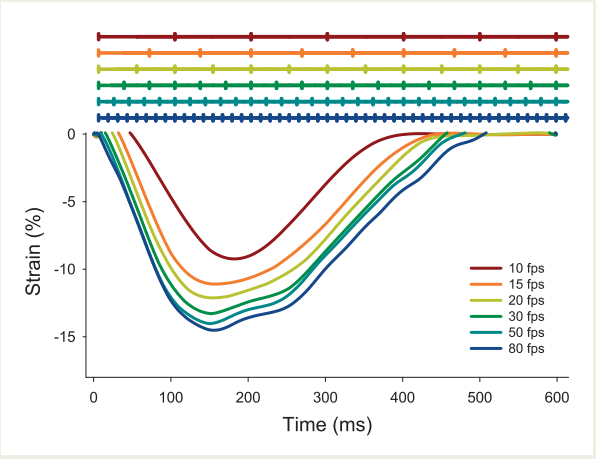

Figure 4 Influence of temporal resolution on strain measurement (data extrapolated from a high temporal resolution STE image undersampled at lower frame rates).

Imaging modality related factors

A first set of factors potentially influencing deformation quantification is the *quality of the acquisition process*, varying between operators and modalities. Ensuring reproducible and accurate breathing control is therefore a key requirement for all modalities.

A second set of modality-dependent factors relate to the *spatial and temporal resolution* of the images. Both resolutions are crucial to ensure the complete characterization of myocardial deformation over successive time frames. If the temporal and spatial resolution is too low (*Figure 4*), the local patterns may become less comparable, an effect known as image de-correlation and displacements may become harder to detect.[19] Precisely, the temporal resolution of cMR and 3DSTE is lower than that of 2DSTE, and inferior to Tissue Doppler Imaging for example, meaning that cMR and 3DSTE are more prone to miss the short-lived events during the isovolumic period. Another parameter that may influence strain values is the reference method. For instance in tagged images, tag deposition is delayed relative to electrocardiogram signal detection, which leads to underestimation of strain (*Figure 5*). On the other hand, STE has a higher spatial resolution than cMR, which is however blunted by a low signal-to-noise ratio. The particularity of the spatial resolution of the ultrasound images is a lower lateral than axial resolution and lower in-depth resolution.[39] This means that most reliable results are obtained closer to the centre line of the image, at smaller depths.

Finally, a last source of potential discrepancies in 2D regional deformation values between modalities is the difficulty to match myocardial segments. This *segmentation misalignment between imaging modalities* is explained by the fact that 2D imaging planes are not necessarily the same when acquired by echocardiography and cMR due to different scanning angles, therefore, complete correspondence between segments is not achievable. For any 2D technique, the pattern within a region of interest is detected and tracked along the image plane. However, as LV deformation is a 3D phenomenon, involving a combination of apex-to-base shortening and simultaneous twisting, the myocardial patterns have a complex 3D motion. Therefore, the pattern within a region of interest defined in a 2D image plane, might move out of the scanning plane during the cardiac cycle. Moreover, unlike cMR, the imaging planes of 2D echo might not depict the true apex in long- and short-axis views, effect known as foreshortening. The through-plane motion and foreshortening represent a limitation of 2D analysis, which are overcome by 3D techniques.

Software-related factors

Several factors related to the specificities of implementing image tracking algorithms can also heavily influence deformation values.

ST algorithms apply *spatial and temporal smoothing* to regularize the results in order to reduce noise, which can affect the measurement robustness by missing significant localized abnormalities in the case of spatial smoothing or by masking rapid events in case of temporal smoothing.[19,40] Also, as strain is computed from the spatial derivatives of the displacement, different regularization strategies (thus affecting motion smoothness) can dramatically affect the range of deformation values computed from the displacement field, at least when considering single material points or small regions. Therefore, parameters based on local estimates are more prone to variability than those based on an integrative combination, i.e. global strains are more stable and reliable than segmental strains.

For block-matching algorithms, the *size of the search region* must be carefully tuned.[19] In general, solving for displacements between short distance regions is challenging and may explain why usually RS (computed on the small distance between endo- and epicardium) is less reliable than LS and CS[41] that are computed over larger regions.

Favouring the tracking in a certain myocardial layer, i.e. endocardial rather than transmural could alter the strain values, as given the fibre orientation, the deformation of the endocardial layer is more important than in the mid and epicardial layers. The level of endocardial strain detection by the software is probably the most important factor (*Figure 6*) inducing intra- and inter- modality variability in strain measurement. Importantly, the level of layer detection may also vary among imaging methods. In particular, as mentioned before, tags are

mainly detected in mid-wall, whereas STE mainly follows endocardial markers.

Other software-related factors that introduce variability are:

- *Computation of Lagrangian or Eulerian strain*, as the two formulas (represented in *Figure 4*) will result in slightly different values, with Eulerian strain having higher absolute values (*Figure 7*).
- *Calculation of global strain values*, either by using the entire myocardial length or by averaging values computed at segmental level, will give different results.[42]

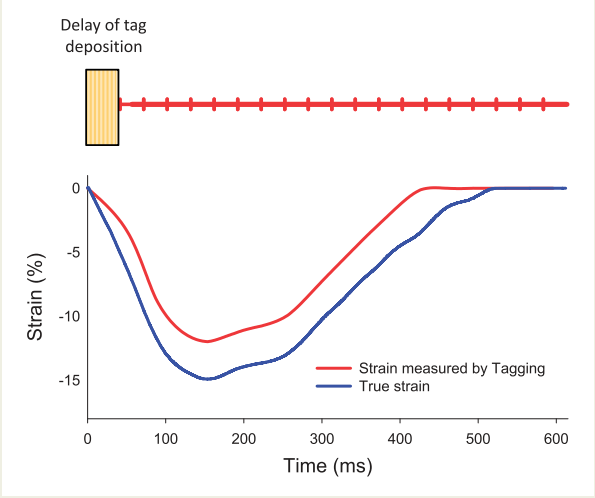

Figure 5 Influence of tag deposition delay of strain computation in cMR tagging [data extrapolated from a high resolution STE image acquired at high heart rate (120 bpm)].

- *Definition of ED and ES*, which has been shown to have a major influence on the accuracy of strain measurements, up to the point that changing ED or ES by only four frames can significantly impact strain values to as much as 20–40% relative changes in ES GLS.[43]

Operator-related factors

Most strain analysis softwares require *manual drawing of the myocardial contours*. As these contours define the regions/points being tracked, different operators contouring differently will obtain different deformation values. For all techniques, operator *experience and training* is an important factor in accuracy of measurements. Indeed most validation studies were performed in highly experienced centres and core-labs and may not translate to overall clinical practice. With the advent of machine learning and fully automated analysis this factor may become less important in the future.

Practical aspects

Tissue tracking software platforms may use different algorithms for measuring deformation and presentation of results, therefore, two aspects become critically important: validation of each specific analysis software and consensus reporting among software package vendors. Validating non-invasive tools used for clinical practice is, however, a challenging task, and has not been done for routine parameters as EF for example. Additionally, EF is subjected to inter-modality (echocardiography vs. cMR) and inter-vendor (different 3DE analysis softwares) variability on top of the suboptimal inter and intra-observer reproducibility.

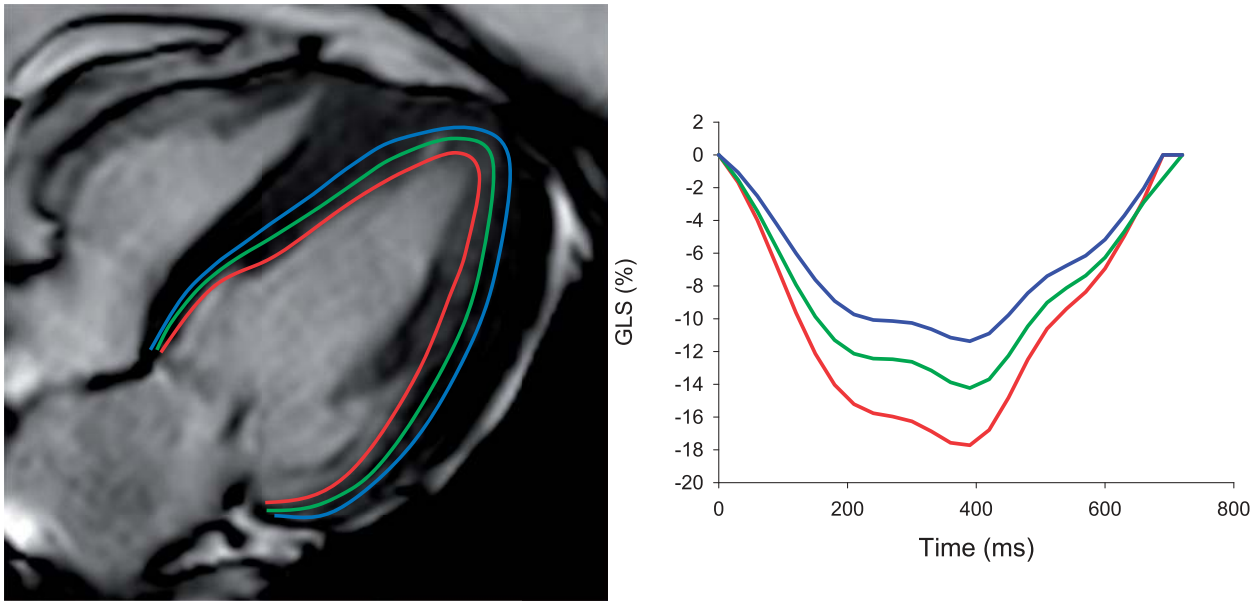

Figure 6 Influence of endocardial layer position on strain measurements. (Example of different layer positions on endocardial strain in a cMR-FT image).

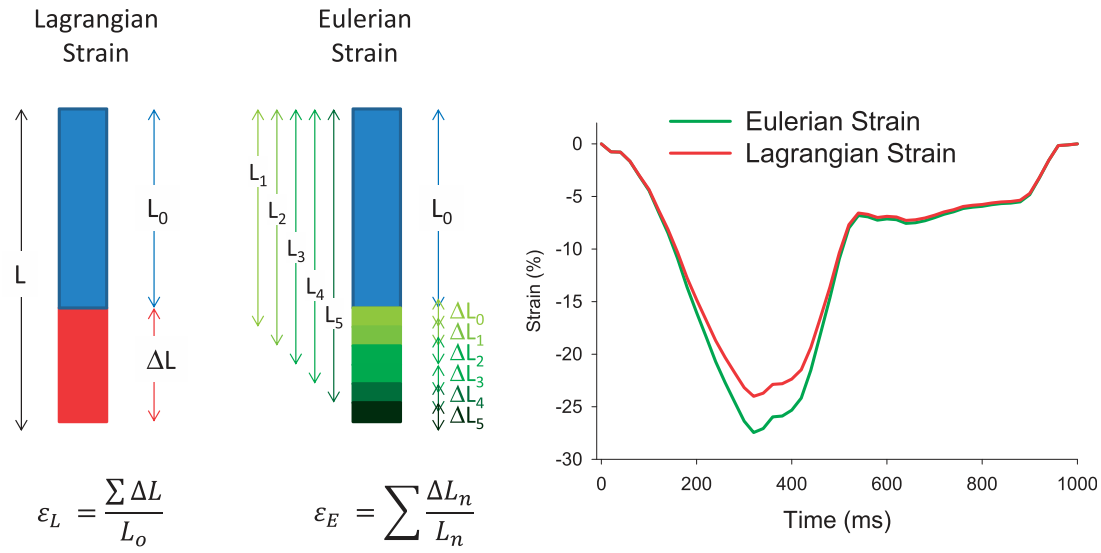

Figure 7 Difference in Eulerian and Lagrangian strain computation.

Table 3 ***In vitro*** **validation of 2DSTE and 3DSTE**

Study	Model	Method	Reference	Software	Strain	Conclusion			
						r/ICC	Bias ± 2 SD (%)	95% CI	
2DSTE									
Korinek *et al.*[44]	Phantom	Different motion rates ($n = 23$)	Sono	GE EchoPAC PC_2D strain,	Long	$r = 0.99$	0.7 ± 2.2	-3.6 to 5	Promising
Amzulescu *et al.*[45]	Phantom	Different motion rates and stroke volumes ($n = 35$)	Sono	Qlab 10.3 Philips	Long	ICC = 0.89	3 ± 2.8	-8.2 to 2.5	Good for Long
3DSTE									
Heyde *et al.*[46]	Phantom	Different motion rates ($n = 7$)	Sono	In-house software	Long	$r = 0.92$			Adequate
					Circ	$r = 0.84$			
					Rad	$r = 0.96$			
Hjertaas *et al.*[47]	Phantom	Different motion rates and stroke volumes ($n = 15$)	Sono	GE EchoPAC BT11	Long	$r = 0.99$	0.8 ± 1.5	-2.1 to 3.7	Accurate for Long and Circ, not for Rad
					Circ	$r = 0.98$	-0.7 ± 1.7	-4 to 2.6	
					Rad	$r = 0.89$	16.1 ± 22.2	-27.4 to 59.6	

Validation

Before implementation in the clinical setting, any new strain imaging method requires a complex process of validation: on synthetic data sets, *in vitro* and *in vivo* experiments, and validation in humans. In opposition to the enthusiastic number of published papers assessing the clinical usefulness of strain, there is a notable lack of validation studies. Indeed, while numerous studies have performed inter-technique comparisons, which can only demonstrate their relative performance, true validation studies for STE, and cMR-FT studies have only been performed for few commercial softwares of the numerous available alternatives. Additionally, most of the clinical validation studies have included a very small number of subjects in the healthy control group and even smaller number in the diseased group, which can only hardly represent the diverse pathological phenotypes encountered in clinical practice.

Validation on synthetic data sets

Synthetic data sets are computer generated images and constitute the first step when testing a new software. In such a controlled environment, the deformation values to be measured are known (i.e. ground truth), while parameters as motion rate, wall thickness and EF can be synthetically altered to simulate different cardiac conditions.

Table 4 ***In vivo*** **validation of 2DSTE and 3DSTE**

Study	Model	Method	Reference	Software	Strain	Conclusion			
						r/ICC	Bias ± 2 SD (%)	95% CI	
2DSTE									
Korinek *et al.*[44]	16 pigs	Baseline, LAD ligation	Sono	GE EchoPAC PC_2D strain	Long Circ	*r* = 0.94	-1.1 ± 7.5	-15.8 to 3.9	Promising
Toyoda *et al.*[51]	6 dogs	Dobutamine	Sono	US customized software	Rad	*r* = 0.92			Promising
Langeland *et al.*[52]	5 sheep	Baseline, CX ligation, esmolol, dobutamine	Sono	In-house software (SPEQLE 2D)	Long Rad	ICC = 0.80 ICC = 0.72	0.4 ± 2.7 2 ± 4.6	-5 to 5.8 -7.1 to 11	Promising
Amundsen *et al.*[53]	9 dogs	Baseline, saline loading, LAD occlusion	Sono	MathLab-based custom made programme	Long Rad	*r* = 0.9 *r* = 0.79		-4.4 to 5 -5.6 to 5.1	Accurate
Reant *et al.*[54]	10 pigs	Baseline, LAD occlusion, dobutamine	Sono	GE EchoPAC	Long Circ Rad	ICC = 0.93–0.96 ICC = 0.50–0.73 ICC = 0.98			Real potential
Pirat *et al.*[55]	7 dogs	Baseline, LAD occlusion, esmolol, dobutamine	Sono	Siemens VVI	Long Circ	*r* = 0.83–0.90 *r* = 0.88–0.94			Accurate
Heyde *et al.*[56]	5 sheep	Baseline, CX ligation, esmolol, dobutamine	Sono	GE EchoPAC v110.0.0,	Long Circ Rad	*r* = 0.69 *r* = 0.72 *r* = 0.64	-2.1 -7.7 18.5	-9.5 to 5.3 -19.5 to 4.1 -4.6 to 41.7	Circ and Radial overestimate
3DSTE									
Seo *et al.*[57]	10 sheep	Baseline, LAD ligation, dobutamine, propranolol	Sono	Toshiba 3D wall motion tracking	Long Circ Rad	*r* = 0.89 *r* = 0.90 *r* = 0.84			Reliable
Heyde *et al.*[58]	14 sheep	Baseline, CX ligation, dobutamine, esmolol	Sono	In-house STE software	Long Circ Rad	*r* = 0.64 *r* = 0.62 *r* = 0.69			Acceptable accuracy
Bouchez *et al.*[59]	13 sheep	Baseline, dobutamine, CX occlusion	Sono	Slemens eSie volume mechanics	Long Circ Rad	*r* = 0.78 *r* = 0.71 *r* = 0.30	-5 ± 6 -5 ± 7 15 ± 19		Good for Long and Circ, less accurate for Rad

Currently, open-access libraries of 2D and 3D simulated ultrasound datasets, as well as simulated cine cMR, are being built to facilitate performance analysis of different software packages in order to promote quality assurance.[48–50] The tested strain imaging methods have shown promising results, and efforts have been made to reach the level of realism of the real ultrasound and cMR images.

In vitro validation

The next step used for validation of strain techniques is by using physical cardiac phantoms in which motion is mechanically controlled. In this case, the motion of the phantom is compared to the ground truth obtained by sonomicrometry recordings. Sonomicrometry is a technique of measuring distances between piezoelectric crystals based on the speed of acoustic signals through the medium they are embedded in. Both 2DST[44] and 3DST[46,47] methods have been validated *in vitro* and have shown good accuracy (see *Table 3*), while for FT there is currently no validation on phantoms.

However, the models used to mimic motion are generally simple and do not represent the true complex cardiac deformation, while cardiac anatomic structures as trabeculations/valves are not represented.

In vivo validation

In order to approximate the real-life conditions, an *in vivo* design to validate strain measurements is required. Different open-chest animal models have been used and myocardial deformation values have been compared to sonomicrometry. Studies investigating 2DSTE and 3DSTE (*Table 4*) have reported overall good agreement of strain by STE with sonomicrometry measurements. Generally, while LS 2DSTE seems to perform well across studies, recent reports describe suboptimal correlation and larger bias for CS and RS by

Table 5 Clinical validation of 2DSTE, 3DSTE, and cMR-FT

Study	Patients	Method	Reference	Software	Strain	Conclusion			
						r/ICC	Bias ± 2SD (%)	95% CI	
2DSTE									
Amundsen *et al.*[53]	7 MI, 4 NL		cMR tagging	MathLab-based custom made programme	Long	$r = 0.87$		-9.1 to 8	Accurate
Cho *et al.*[60]	30 CAD		cMR tagging	GE EchoPAC BT04	Long	$r = 0.51$	2 ± 5.5	-13 to 8.7	Modest performance
					Circ	$r = 0.64$	0.7 ± 5.4	-10.9 to 9.9	
					Rad	$r = 0.60$	0.4 ± 9.5	-19.3 to 18.5	
Bansal *et al.*[61]	30 CAD		cMR tagging	GE EchoPAC-PC v6.0	Long	$r = 0.5$			Feasible
					Circ	$r = 0.63$			
					Rad	$r = 0.59$			
Amundsen *et al.*[62]	10 MI, 11 NL		cMR tagging	GE EchoPAC-PC v6.0	Long	$r = 0.65$		-8.1 to -13	Suitable
				In-house STE software		$r = 0.59$		-12 to -11	
Amzulescu *et al.*[45]	75 DYS , 30 HCM, 31 NL		cMR tagging	Philips QLAB 10.3	Long	ICC = 0.89	-4.9 ± 3	-10.5 to 0.8	Best for GLS, suitable for GCS, suboptimal for segmental strain
					Circ	ICC = 0.80	-5.2 ± 5.3	-15.4 to 5.3	
3DSTE									
Kleijn *et al.*[63]	45 NL	Mid-ventricular	cMR tagging	Toshiba 3D wall motion tracking software	Circ	0.8	10 ± 1.7	6.7–13.2	Circ overestimates strain
Zhou *et al.*[64]	12 NL, 12 DCM, 11 HTA	Apical and mid-ventricular	cMR tagging	Slemens eSie Volume Mechanics	Circ	0.89	1.4	-9.4 to 12.2	Feasible
						0.91	-0.2	-8.7 to 8.4	
Amzulescu *et al.*[65]	63 DYS, 27 HCM 91 NL		cMR tagging	Philips Prototype software	Long	ICC = 0.89	0.5 ± 2.3	-4.1 to 5.1	GLS, GCS accurate, suboptimal for segmental strain
					Circ	ICC = 0.83	0.2 ± 3	-5.6 to 6.1	
cMR-FT									
Hor *et al.*[66]	191 Duchenne muscular dystrophy, 42 NL	Mid-ventricular	cMR tagging	TomTec Diogenes	Circ	0.89		-4 to 3.5	No under or overestimation.
Harrild *et al.*[67]	13 NL, 11 HCM	Mid-ventricular	cMR tagging	Customized software programme (Cardiotool)	Circ		1 ± 9	-16.6 to 18.6	No under or overestimation.
Augustine *et al.*[68]	145 NL	20 NL had cMR tagging	cMR tagging	Tomtec 2D Cardiac Performance analysis	Long		-1	-16 to 3	Long and Rad overestimate
					Circ		-0.7	-6 to 4	
					Rad		11	-1 to 23	
Wu *et al.*[69]	10 NL + 10 left bundle branch, 10 HCM	Endocardial and mid-wall layer	cMR tagging mid-wall	TomTec Diogenes	Circ	Segmental Mid FT ICC: 0.58 (0.14–0.80)			Circ overestimates, segmental FT unreliable.
Moody *et al.*[70]	35 NL + 10 DCM	Endocardial layer	cMR tagging endo-, mid-, epi-, transmural	TomTec Diogenes	Long	0.70	1.3 ± 3.8		Sufficient agreement.
					Circ	0.83	0.2 ± 4		
Singh *et al.*[71]	18 aortic stenosis	Endo, endo/epi average	cMR tagging	TomTec Diogenes	Long	ICC = 0.54	3.6 ± 3.3	-2.9 to 10.2	Long and Circ overestimate
					Circ				

CAD, coronary artery disease; DCM, dilated cardiomyopathy; DYS, dysfunction; HCM, hypertrophic cardiomyopathy; MI, myocardial infarct, NL, normal, healthy volunteers.

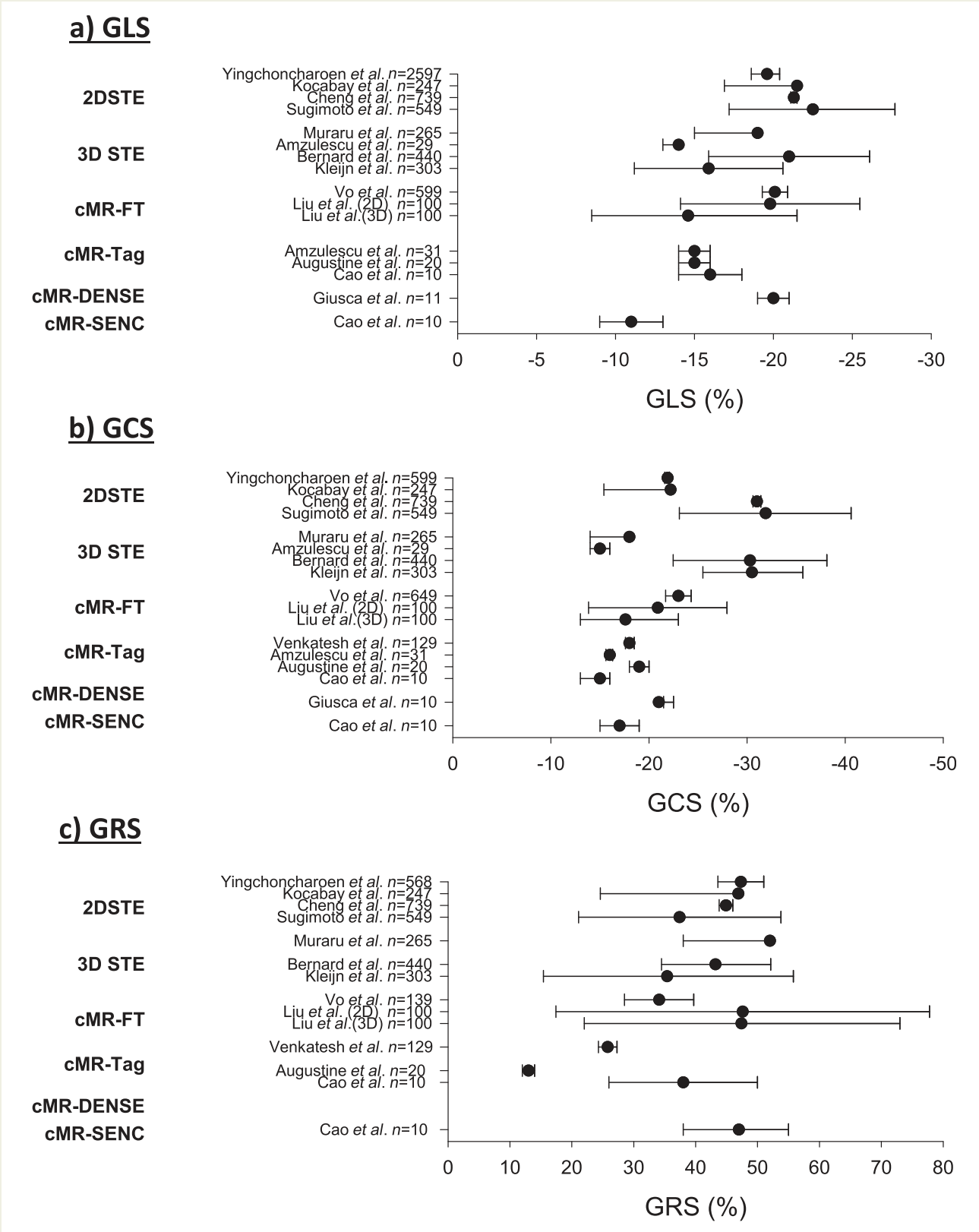

Figure 8 Reported normal (mean and 95% confidence interval) global strain values in healthy subjects for different imaging modalities. Data from refs.[45,65,68,82–91] Normal GLS, GCS, and GRS values were compared using random effects models weighted by inverse variance and heterogeneity between methods was compared using the Cochran Q test and the inconsistency factor. For all strain measurements, I^2 and Q indicated significant heterogeneity among studies and methods.

2DSTE.[56] For 3DSTE, LS and CS are accurate compared to sonomicrometry, while RS has been shown to be less reliable.[59] To date, FT has not been tested *in vivo*.

Similar to the *in vitro* validation, this approach allows measurement of deformation in only a few LV regions, where the sonomicrometry crystals are located, and image quality is better than in standard clinical settings, therefore, not representative.

Clinical validation

Unlike *in vitro* and *in vivo* settings, image quality is different and motion can be calculated in more than one region for all strain components. Clinical validation in humans is achieved by using another previously validated imaging modality, such as cMR tagging, as reference framework. Studies investigating the reliability of speckle and tissue tracking techniques compared to cMR tagging in humans have shown lower accuracy than for the pre-clinical validation, but generally demonstrated satisfactory results (*Table 5*). Four studies compared commercial[45,60,61] or custom developed *2DSTE*[62] vs. cMR-tagging with modest to good correlations and acceptable bias. However, it was not always performed for all strain directions[45,60,61] but most often only for LS.[62] Correlation was acceptable for GLS, but less for GCS and importantly agreement was poor at regional level.[45] In addition, there was overestimation of LS and CS and spatial inhomogeneity in particular at apical level. *3DSTE* has been compared to cMR tagging by three studies evaluating the CS direction in healthy controls[63] and small number of diseased,[64] using software from two different manufacturers or prototype software.[65] While the correlation was good, one study found that CS was overestimated by 3DSTE.[63] Another study found better agreement of 3DSTE than 2DSTE with cMR tagging.[65] Part of the inter-modality differences have been largely attributed to the technical specifications of each software,[45,65] namely the tracking algorithms, which, despite contouring transmural regions of interest, may lead to higher deformation values when endocardial layer is predominantly tracked than when a transmural approach is favoured. Additionally, most clinical studies have assessed global strains, and the few attempting to validate segmental strain in patients[45,53,65] show conflicting results, the most recent ones questioning the reliability of regional deformation assessment.[45,65]

For *FT*, reports of the clinical validation data vs. cMR tagging are conflicting, with some studies showing good agreement,[66,70] while others describe strain overestimation of certain strain deformation directions.[68,69,71] Similar to STE, it has been generally concluded that segmental deformation assessment with FT is less reliable than global strain estimation.[69]

Intervendor agreement

An increasing number of studies evaluating differences between STE software manufacturers have consistently reported significant intervendor variability for 2D GLS measurement.[72–76] Therefore, the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) have set up a task force to assess sources of STE measurement variability in partnership with the industry,[42] aiming to standardize STE in order to potentially extend its clinical application. Subsequent to the task force initiative, different manufacturers have released improved software versions and the inter-vendor agreement for 2DSTE GLS has improved.[77,78] However, 2D regional STE measurements are still subject to important variability among vendors.[78,79]

Intervendor agreement has been investigated for 3DSTE as well and, similar to 2DSTE, strain measurements were discordant, depending on the tested imaging equipment and analysis software. While GLS seemed less affected, GCS had acceptable intervendor agreement and GRS had the highest variability.[80]

A similar issue is anticipated for FT, as inconsistencies between the commercially available softwares have been demonstrated, with acceptable differences for GLS and GCS, but considerable disagreement for GRS.[81,82]

Therefore, variations in proprietary software are responsible of suboptimal intervendor agreement of strain measurements and constitute a significant limitation to the implementation of STE and FT techniques. Cross-platform standardization is needed in order to expand deformation imaging methods beyond the current research oriented environment.

Normal strain values

The application of myocardial strain to quantify deformation in pathological states requires the definition of a normal range. As shown by *Figure 8*, reported normal ranges vary largely between the different deformation imaging modalities. In particular, heterogeneity was larger for GRS than GLS and GCS. Besides the technical factors described above, patient-related factors (age, gender, and ethnicity) and haemodynamic factors (heart rate and blood pressure) constitute other potential influences.[83,84,92]

Clinical implications

For the aforementioned reasons, in clinical practice, a global strain parameter rather than a segmental strain value should be favoured when estimating LV function. And, as the reported technical limitations, validation issues and intervendor agreement pertain particularly to GCS and GRS, and less to GLS, the preferred global strain parameter should be GLS. Additionally, baseline and follow-up strain measurements need to be obtained using the same modality, analysis system, and software version. As deformation estimation techniques are less dependent on segmentation variability than EF calculation, strain measurements have proven to be more reproducible than EF.[93–95]

Therefore, when facing two imperfect parameters of systolic function estimation, i.e. EF and strain, the clinician should take into account the potential benefits and disadvantages of each.

Conclusion

While multiple studies have shown the usefulness of strain quantification for risk stratification in various cardiac disease,[9,39] the main limitation remains that strain values vary among methods, modalities and software version.[96] Therefore, method and software specific cut-off values need currently to be used. Another major caveat, which

remains largely neglected, is the lack of proper validation of most methods vs. absolute and objective reference standard.

To allow accurate deformation estimates and avoid unnecessary variability between products and methods, it should be mandatory that each strain quantification method undergoes rigorous validation using a multi-step process before wide-use for research purposes, and even more, for clinical implementation. Despite the difficulties, such an approach of widespread validation and cross-modality and vendor standardization needs to be applied to allow further development of this technology and successful clinical utilization of these methods.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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