# 4D Strain – A clinical viewpoint

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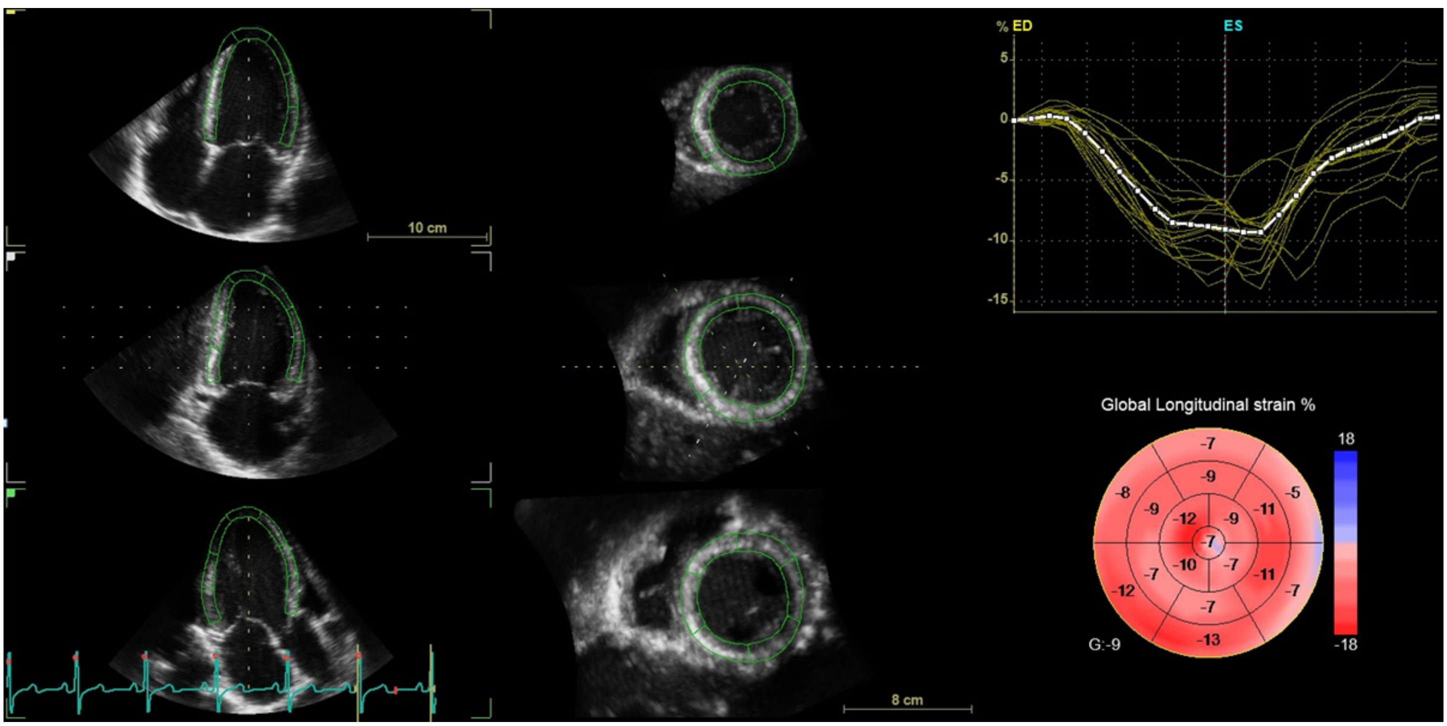

# 4D Strain – A clinical viewpoint

Four-dimensional (4D) Strain is a novel analysis method designed for left ventricular (LV) myocardial deformation analysis based on 4D LV data sets. 4D Strain integrates speckle-tracking with three-dimensional echocardiography, enabling the computation of all LV Strain components from a single apical LV 4D data set. In comparison with two-dimensional (2D) speckle-tracking, 4D Strain seems potentially more adequate to capture the complex LV deformation with no issues related to the “out-of-plane” motion of speckles or need to interpolate the whole LV myocardium from the partial information contained in three thin slices of the LV (Figure 1).

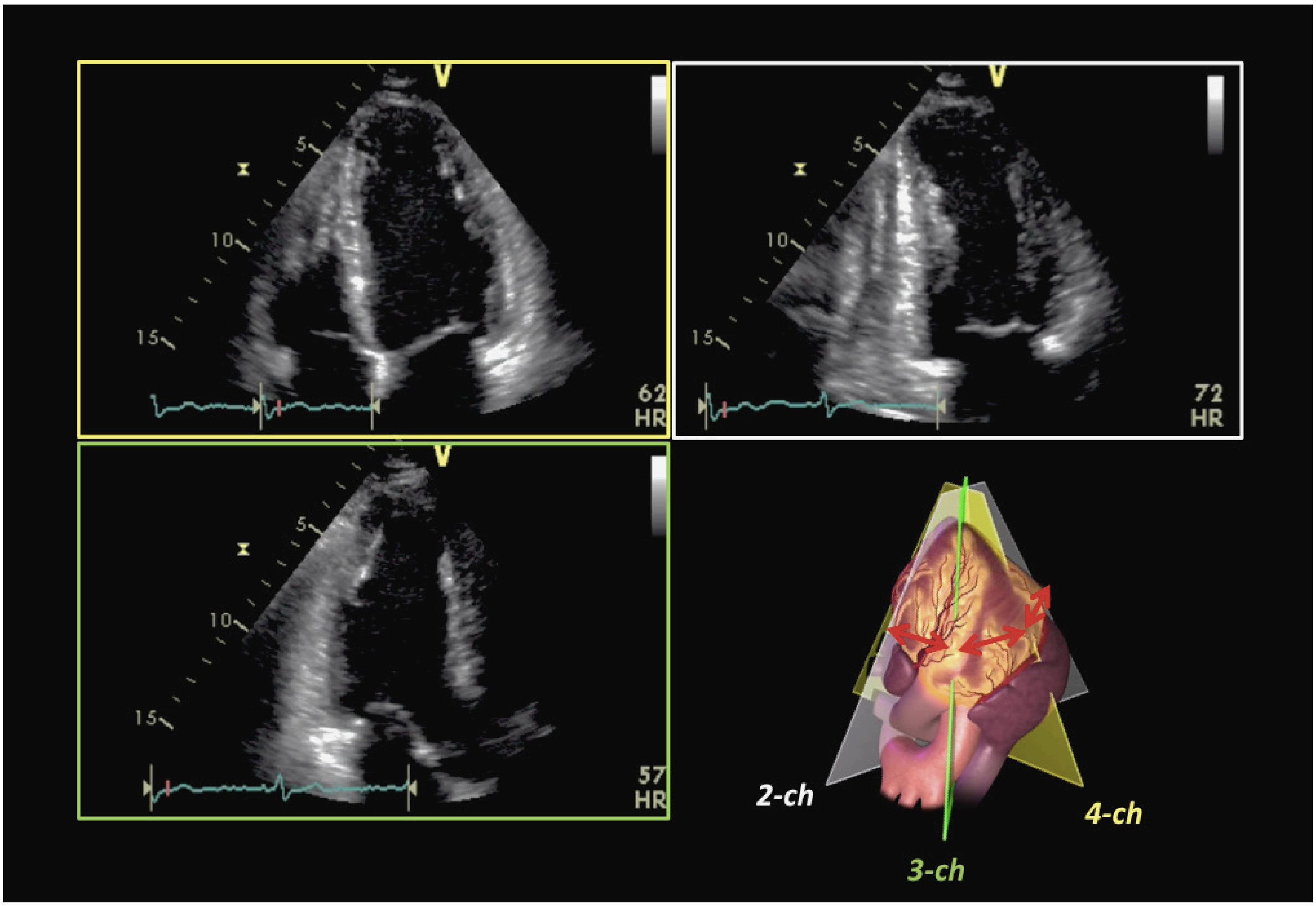


Figure 1. Echocardiographic two-dimensional (2D) acquisitions of the left ventricle for 2D longitudinal strain analysis. The three apical 2D views (4-chamber – yellow quadrant, two-chamber – white quadrant, and long-axis – green quadrant) display only a very limited part of the myocardium, which is confined in three thin slices sharing the same longitudinal axis of the left ventricle (bottom right). As a consequence, longitudinal strain analysis by 2D speckle-tracking (AFI/2D Strain): (I) reflects deformation abnormalities only if they are captured by the three standard 2D slices, and may miss them if the pathologic area lies in between views (red arrows); (II) is highly dependent on the cut-plane used in the 2D acquisition (since there are no precise anatomical references for the three views, slightly different cut-planes of the left ventricle by probe rotation or apical foreshortening may show the same pathologic area in various extents and, hence, with different strain results). In contrast, 3D volumetric acquisition of the left ventricle enabling speckle-tracking in the 3D space obviates for these issues.

| AFI/2D Strain | 4D Strain |
|---|---|
| three apical 2D planes | one apical 4D volume |
| 40-80 fps[1] | >25 vps (optimally 30 to 40)[1] |
| regular heart rate (consecutive 2D LV planes) | regular heart rate (ECG-gated 4D LV full-volume) |
| all strains (longitudinal, radial, circumferential)[8] | all strains (longitudinal, radial, circumferential) |
| no two-directional strain | two-directional (area) strain[2] |
| static bull's eye[3] | dynamic bull's eye[3] |
| non-simultaneous segmental peaks[4] | simultaneous segmental values[4] |
| positive peak rule[5] | no positive peak rule |
| drift compensation[6] | no drift compensation |
| end-systole: time of aortic valve closure | end-systole: time of LV minimal volume[7] |
| tracking quality check: more automated | tracking quality check: more reliance on user |

Table 1. Comparison between AFI/2D Strain and 4D Strain

[1] at regular heart rates; higher temporal resolution is advisable in tachycardia to avoid undersampling.
[2] reflects a combination between longitudinal and circumferential strain.
[3] AFI/2D Strain displays one snapshot with peak values of segmental strain; 4D Strain displays simultaneous segmental strain values continuously throughout the cardiac cycle.
[4] with AFI/2D Strain, peak segmental values are displayed irrespective of their reciprocal timing during systole; with 4D Strain, simultaneous segmental strain values are displayed in each frame.
[5] in the Bull's eye display, a positive strain is displayed during systole for a certain segment, only if the positive peak strain exceeds 75% of the peak negative strain value in the same segment[6].
[6] all segmental strain curves are "forced" by the software to return to baseline at end-diastole. Abbreviations: 2D, two-dimensional; fps, frames per second; LV, left ventricular; vps, volumes per second.
[7] the correct timing of end-systole should be verified and corrected in the Volume Waveform stage (not only in the ESV stage), as this directly affects the end systolic strain values.
[8] AFI and 2D Strain of apical view images provide only longitudinal strain, while 2D Strain of SAX view provides circumferential and radial strain.

| LV parameters | median % | $1^{st}$ - $3^{rd}$ quartiles |
|---|---|---|
| 2D Longitudinal strain | -21 | -20 to -23 |
| 2D Circumferential strain* | -22 | -20 to -24 |
| 2D Radial strain* | 46 | 39 to 54 |
| 4D Longitudinal strain | -19 | -17 to -21 |
| 4D Circumferential strain | -18 | -17 to -20 |
| 4D Radial strain | 52 | 47 to 59 |
| 4D Area strain | -33 | -31 to -36 |

Table 2. Reference ranges for left ventricular AFI/2D Strain and 4D Strain values, obtained from 265 healthy subjects (age range 18-76, 57% women), with no cardiovascular risk factors, no evidence of cardiovascular disease and no medication[19].

* Global 2D circumferential and radial strain values were calculated by averaging the LV segmental strains obtained at midventricular short-axis level

## Comparison with AFI/2D Strain speckle-tracking tool

There are several differences between AFI (Automated Function Imaging)/2D Strain and 4D Strain in acquisition and analysis (Table 1). Even though both reflect the same phenomenon (i.e. myocardial deformation in longitudinal base-to-apex direction), the differences in spatial and temporal resolution, algorithm, strain computation and display between the two softwares usually account for slightly lower absolute values of 4D versus 2D longitudinal strain[1]. As a consequence, the normal range reported for AFI/2D Strain longitudinal strain[2] cannot be used in 4D longitudinal strain, and specific reference values for the latter should be identified as well (Table 2)[3]. For circumferential and radial strain, 4D Strain has been shown to provide more reproducible measurements than 2D Strain[4].

There are also differences in terms of algorithms and definitions of strain parameters among various vendors[5]. GE Healthcare is participating in the EACVI/ASE strain standardization initiative to overcome this issue. Many labs have several years of experience with speckle tracking 2D Strain. To start using 4D strain It will be very useful for the users to have information about the expected differences between 2D and 4D Strain. Also, there is a strong need to have an overview of differences between 4D Strain from the different vendors. However, this paper pertains only to the speckle-tracking technology developed by GE Healthcare.

# Practical user guide

### Patient selection

Good image quality and temporal resolution (i.e. volume-rate) are key requirements for an adequate speckle-tracking analysis. Before proceeding to perform 4D Strain analysis, make sure that your patient:

- Has a good 2D acoustic window from the apical approach
- Is in sinus rhythm with a stable cycle length
- Is able to cooperate for respiratory maneuvers, including breathholding for several seconds

**Practical tip**

Pay special attention to the quality of the electrocardiographic (ECG) tracing: adjust the position of the electrodes and choose the lead (from PHYSIO menu) that displays the smoothest trace, with well-defined R/Q waves and minimal noise; avoid traces with prominent P or T waves, as these will interfere with the gating during 4D data set acquisition.

### Acquisition of LV 4D data set

- Use a cutout bed and ask the patient to assume left lateral position with his left arm raised above the head, in order to widen the intercostal spaces and facilitate acoustic access.
- Place the 4V-D transducer in the apical region and choose the position that shows the best definition of endocardial and epicardial LV borders in 4-chamber view. Apply gentle pressure and, differently from conventional 2D imaging, favor the best image definition of the LV wall and pay less attention to apical foreshortening by using a higher than usual intercostal space.
- Align the TGC buttons in a straight line above 50% for a proper visualization of the LV walls; make sure to avoid undergaining, especially at the apical region.
- Press 4D, select the Large volume size preset and, if necessary, increase it further (by manually rotating the VOLUME SIZE knob) to accommodate the LV apex. Be aware of the trade-off between volume size and temporal resolution, as too low temporal resolution (<25 vps) will result in an unreliable 4D Strain analysis.
- Select the number of cycles for multi-beat acquisition modality: you may choose 4 cycles for normal LVs, and 6 cycles if the volume size had to be manually increased (because of enlarged LVs) or if the heart rate is faster than normal.

**Practical tip**

4D LV full-volumes obtained from less than 4 cycles will generally provide unacceptably low temporal resolution for 4D Strain analysis. Temporal resolution should be increased by selecting the minimum volume size able to accommodate the LV, adjusting image depth in order to maximize the LV, and increasing the number of cardiac cycles to acquire. We do not recommend to manually increase the temporal resolution (FRAME-RATE knob), as this will reduce the scan line density and lower the quality of the speckles.

- Image optimization is critically important before acquisition: fine refinements in transducer position (by translation, rotation or tilting) and observing the changes in image quality during respiratory maneuvers (apnea in either full inspiration, full expiration or in any moment between) are recommended. We also recommend performing this image optimization while observing the LV 12-slice display, which allows for a comprehensive overview in real-time of whether all LV segments will be included and properly visualized within the upcoming data set.
- Keep the transducer still, ask the patient to stop breathing when the image is optimal and press **MULTI-BEAT** touch button, then wait for at least 4/6 consecutive cycles to be acquired while watching for the occurrence of stitching artifacts. If the patient tolerates, a longer apnea may allow the selection of another set of 4/6 from remote cycles with no stitching artifacts (**CYCLE SELECT**). Otherwise, the full-volume acquisition must be re-attempted.

**Practical tip**

Ideally the 4D LV data set should have a good endocardial definition and blood-tissue contrast, a good temporal resolution (30-40 vps, or a temporal resolution greater than 40% of the patient's heart rate), no visible stitching artifacts or reverberations, and a proper visualization of the entire wall thickness in all LV segments (Figure 2).

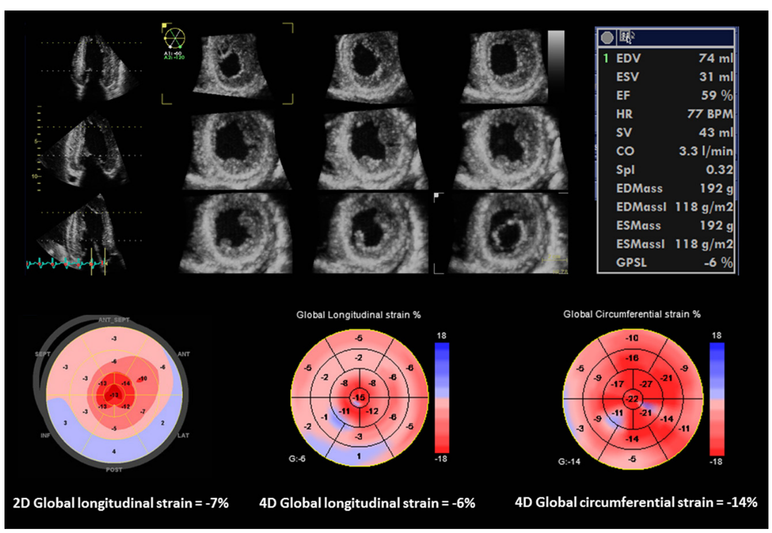


Figure 2. Comprehensive assessment of left ventricular function by 4D AutoLVQ in a 49-year-old patient with restrictive cardiomyopathy (amyloidosis). Left upper panel illustrates the 4D left ventricular full-volume in 12-slice display, showing a diffusely increased thickness and echogenicity of the myocardium in all segments. Quantitative analysis demonstrates left ventricular abnormalities typical for cardiac amyloidosis: small volumes and reduced stroke-volume with preserved ejection fraction, increased mass, severe reduction of 4D longitudinal strain (also detected by AFI/2D Strain performed in the same patient on 2D images - bottom left), which is impaired relatively more than the 4D circumferential strain basal and mid left ventricular segments typically show lower strain values than the apical region (relative apical sparing).

### Analysis and interpretation of 4D strain results

- Select 4D AutoLVQ from the **MEASUREMENTS** menu and follow the workflow steps required for 4D volumes and strain quantification. Manually verify and adjust, if necessary, the timing of end-diastole and end-systole (**FRAME** knob).
- Use the semiautomated endocardial border identification, with manual initialization of endocardium by placing several points to apex and mitral annulus in each of the 3 LV apical views.

**Practical tip**

The automated method, although faster and with no reliance on the operator, may result in less accurate measurements of LV volumes (underestimation) than the semiautomated method, i.e. endocardial contours are manually initialized and edited[6]. During editing, verify the position of the endocardial contour in each segment, including in between standard views (LOCK VIEW and ROTATE VIEW functions) both in still frames and in motion (by pressing the 2D button).

- Apply manual editing in both end-diastolic and end-systolic frames, individually: first onto the endocardial border, to include trabeculae and papillary muscles within the LV cavity; second time onto the epicardial border, to fit the whole thickness of the LV wall in every segment (Figure 3). It is more practical to start the editing from the apical region and then follow with the more basal part of the LV.
- In addition to the automated quality check of segmental tracking performed by the software (rejecting segments that show excessive drift at end-diastole)[7], perform also a visual check and validate or reject individual segments by assessing: (I) motion tracking in the LV views displayed aside; (II) corresponding regional curve patterns (if unsound, especially of basal inferior and basal infero-lateral segments where suboptimal tracking may occur).
- The correct timing of end-systole should be verified and corrected in the Volume Waveform stage (not only in the ESV stage), as this directly affects the endsystolic strain values.

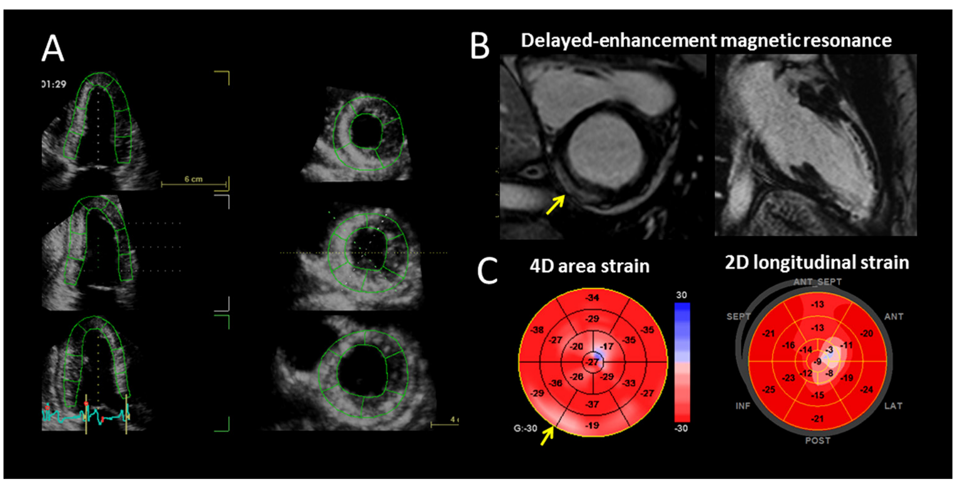


Figure 3. Left ventricular deformation analysis (4D area strain and 2D longitudinal strain) in a 37-year-old patient with no classical risk factors, presenting with signs of anterior myocardial infarction due to an occlusion of the left anterior descendent coronary artery. A, Region-of-interest (ROI) for 4D Strain analysis, covering the entire wall thickness in three dimensions and displayed in 3 apical and 3 short-axis views of the left ventricle. B, Contrast-enhanced magnetic resonance imaging showed transmural necrosis in anterior segments and a second region of delayed enhancement (arrow) localized at the basal infero-posterior segments at epicardial level interpreted as focal myocarditis. C, Deformation analysis shows reduced strain in the infarcted antero-apical segments, but only the analysis of area strain (combining longitudinal and circumferential deformation) by 4D Strain has identified regional abnormalities in the infero-posterior basal region of the left ventricle in this case (arrow, left image). In contrast, 2D longitudinal strain by AFI/2D Strain, which mainly reflects subendocardial function, has not identified any abnormality in infero-posterior region, but clearly delineated the infarcted region (right image).

## Validation

Despite being very promising, the theoretical advantages of the 4D Strain over the 2D speckle-tracking approach could be outweighed by the technical challenges derived from using a volumetric acquisition of the LV. Therefore, more clinical experience will be useful to better decide how 4D Strain can be best utilized clinically. The validation process of 4D Strain is rather difficult, due to the lack of an adequate 3D gold standard that can be applied noninvasively in human subjects[10]. A phantom study[11] reported a very good accuracy of 4D longitudinal and circumferential strain against sonomicrometry, at a slightly lower temporal resolution (36.6 vps) than recommended for 2D speckle-tracking (50-80 fps).

## Potential clinical applications

**Healthy subjects.** A thorough understanding of the normal 4D deformation pattern in normal hearts is fundamental before the clinical application of 4D Strain to study cardiac diseases. Preliminary results on normal values of global 4D Strain components available to date are reported in Table 2. The possible relationship between 4D Strain parameters and age, gender, body size, blood pressure, heart rate etc. needs to be further explored. Furthermore, the characterization of regional strain patterns and base-to-apex gradients is to be reconsidered using 4D Strain, particularly for radial and circumferential strain, as these are more prone to errors with the 2D speckle-tracking approach due to variable/off-axis plane selection and through-plane motion.

**Ischemic heart disease.** 4D echocardiography holds great promise to improve the regional functional assessment by 2D echocardiography, due to several advantages: less influenced by apical foreshortening and variable image plane position; possibility to correct the image plane at any time after acquisition to minimize errors in visual wall motion interpretation; simultaneous quantification of LV volumes, ejection fraction and mass, with the potential of higher accuracy and reproducibility than with conventional 2D methods. In addition, 4D speckle-tracking enables the computation of all strain components in a very fast, objective and reproducible way[12]. Preliminary evidence[13, 14] showed that 4D circumferential strain could be useful to identify the segments with transmural infarction in patients with recent ST-elevation myocardial infarction, when compared with visual wall motion score during standard echocardiography (akinesia/diskinesia) and with magnetic resonance (>50% delayed enhancement)(Figure 4). Moreover, 4D longitudinal strain may provide incremental information over clinical and conventional echo indices to predict global LV functional improvement after acute myocardial infarction[15].

**Cardiomyopathies.** Among all diseases involving the myocardium, cardiomyopathies with the ejection fraction within the normal range (hypertrophic cardiomyopathy, amyloidosis, etc.) are particularly attractive to be better characterized and understood using the novel technologies able to quantify myocardial deformation in all directions. In addition, pathologic processes with variable extensions across the myocardial layers (i.e. myocarditis typically involving subepicardial layers, myocardial hypertrophy with early impairment of subendocardial layer, etc.) could be diagnosed early in their course, before a reduction in global ejection fraction becomes apparent, by the relative involvement of different strain components (Figures 2 and 3). Zhang[16] showed that global 4D longitudinal strain may serve as a sensitive indicator of early LV systolic dysfunction in diabetic patients with normal ejection fraction. In addition, 4D area strain could detect the early impairment of LV myocardial systolic function in untreated hypertensive patients[17].

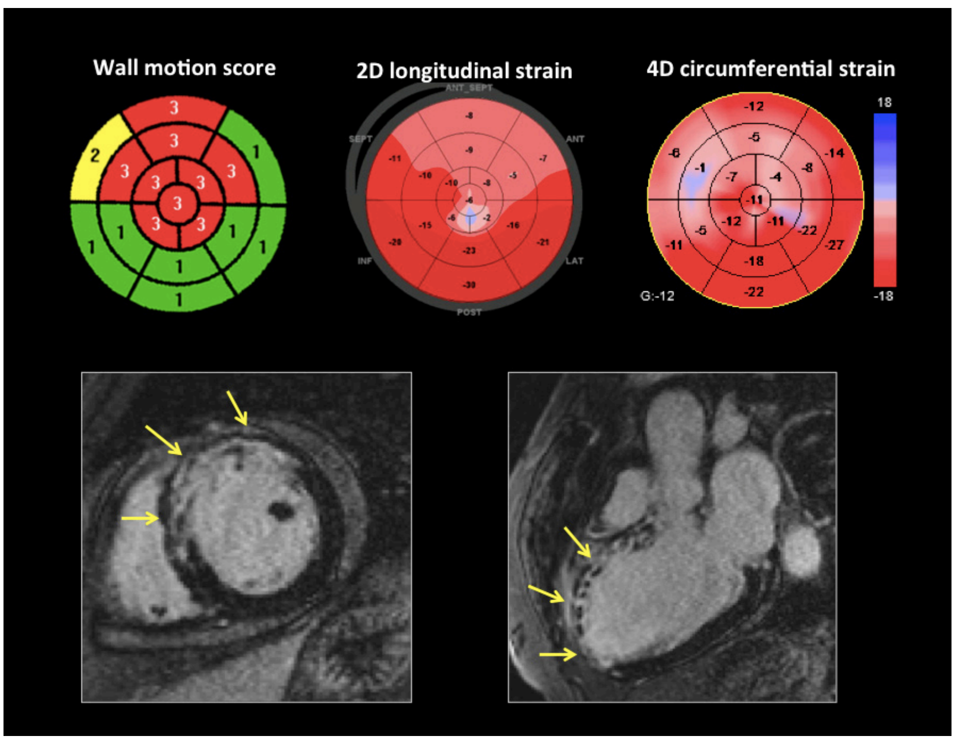


Figure 4. Left ventricular wall motion and deformation analysis in a 62-year-old patient with recent anterior myocardial infarction, presented for comparison with the information provided by delayed-enhancement magnetic resonance. Note the close correspondence between the regional abnormalities outlined by bull's eye displays and the extension of transmural necrosis at magnetic resonance (arrows). Among all 4D Strain components, 4D circumferential strain showed the highest level of concordance with the other methods regarding the localization of segmental abnormalities (Wall motion score: 1, normokinesia; 2, hypokinesia; 3, akinesia).

**Valvular heart disease.** Risk stratification and outcome of asymptomatic patients with severe left-sided valvular heart disease may change, if the inclusion of strain parameters in the decision-making algorithms will be contemplated. LV deformation analysis by 2D speckle-tracking provided incremental information in this subset of patients, identifying early subclinical LV dysfunction and predicting the development of LV systolic function impairment after surgery[18]; no evidence is available at present for 4D strain.

## Current limitations

To avoid any potential misuse of the 4D Strain method it is important to be aware of the following limitations:

- lack of evidence on the prognostic value of 4D Strain in comparison with conventional echocardiographic indices of LV function and AFI/2D Strain
- technical limitations
  - lower feasibility in comparison with other methods due to reliance on good acoustic window, regular rhythm and patient cooperation, susceptibility to artifacts and variations in image quality;
  - relatively low temporal resolution preventing the analysis of diastolic function, limitations in volume size in order to avoid a drop in temporal resolution to unacceptably low levels;
  - drift-based segment rejection which may confound the 4D Strain analysis in localized myocardial diseases, etc.;
  - lack of peak detection in the strain traces, preventing direct comparison with 2D strain

## Conclusion

4D strain is a new echocardiographic tool for estimating myocardial deformation that holds significant promise to improve the accuracy and reproducibility of LV functional quantification, as well as to reduce the subjectivity in visual interpretation of regional wall motion. However, there is a need to gain further clinical experience with the method to decide how to best utilize the method clinically. Eventually an EACVI and ASE initiative for intervendor standardization might be needed for 4D Strain.

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