A comparison between radial strain evaluation by speckle-tracking echocardiography and cardiac magnetic resonance imaging, for assessment of suitable segments for left ventricular lead placement in cardiac resynchronization therapy.

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A comparison between radial strain evaluation by speckle tracking echocardiography and cardiac MRI, for assessment of suitable segments for left ventricular lead placement in Cardiac Resynchronization Therapy

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Abstract and keywords:

Aims: A cut-off of 9.8% maximum speckle tracking radial strain in the segment with the latest mechanical delay has been proposed as predictive for selecting the best left ventricular lead placement for positive response on CRT. However, pacing transmural scar should be avoided, and the purpose of this study was to evaluate the ability of echocardiographic radial strain to predict presence of scar in the left ventricle segments.

Methods: A total of 404 left ventricular segments were analysed, from 34 patients eligible for CRT. Preoperative CMR and echocardiography was performed, and maximal strain values from echocardiography speckle tracking were compared to CMR data.

Results: Hypokinesia and strain values showed a strong correlation ($p<0.001$). Even though segments with CMR verified scar had lower strain values than segments without scar (14.8±7 vs. 16.0±10), the predictive value of the proposed 9.8% cut-off was low (sensitivity 33% and specificity 72%). Scar burden was higher in ischemic patients (13.5% vs. 5.3% $p=0.0001$). Relative difference in strain values (target segment strain compared to the average strain value of the adjacent segments) was higher if there was transmural scar in the target segment as compared to a hypokinetic but viable target segment (87% vs. 38% difference, $p=0.03$).

Conclusion: Speckle tracking radial should ideally be complemented by CMR for accurate assessment of viability, especially for patients with ischemic ethiology of heart failure where transmural scar is more common. Comparison of strain values with the adjacent segments may be helpful for assessing viability.

Keywords:

Cardiac Resynchronisation Therapy, Speckle Tracking, Radial strain imaging, cardiac magnetic resonance, Heart Failure.

Introduction:

Cardiac Resynchronization Therapy (CRT) is a well validated treatment for reducing mortality and morbidity in heart failure refractory to medical therapy and with wide QRS complex [1-4]. However, between 25-40% of the patients do not seem to benefit from the treatment, thus reducing the cost-effectiveness of the treatment overall and exposing these non-responding patients to adverse side-effects without any positive benefit from the device therapy. The cause for non-response is most likely multifactorial, but there is emerging evidence that the placement of the left ventricular lead is important, and recently two randomized prospective trials have showed a significant benefit of targeted LV lead placement in a segment with late mechanical activation (the TARGET study and the STARTER study)[5, 6]. It is mechanistically appealing to select a segment with late mechanical activation for LV lead placement, and the most reliable and only prospectively validated method so far has been radial strain analysis of segment with latest mechanical delay, using echocardiography evaluation by speckle tracking[5]. Strain analysis using speckle tracking is regarded as more robust than standard tissue-doppler based imaging, for determining active contraction within the different cardiac segments [7, 8]. However, cut-off values for determining viable myocardium are inconsistent in different studies, and there is no consensus on this issue. Cardiac magnetic resonance (CMR) is the gold standard for assessing viability by using late gadolinium enhancement to visualize non-viable segments with transmural infarction or fibrosis[9-12]. The present study aims to explore the correlation between radial strain and myocardial viability, and possibly improve the reliability of 2D speckle tracking strain analyses for differentiating between viable left ventricular myocardial segments and scarred segments, in a group of prospectively selected patients receiving CRT devices.

Methods:

34 patients accepted for CRT were prospectively recruited from a tertiary referral centre in Sweden. The only major contraindications were severe renal failure or chronic atrial fibrillation. Patients with insufficient image quality for echocardiographic radial strain evaluation were excluded. Each of the patients underwent echocardiography and cardiac magnetic resonance (CMR) examination within a few weeks prior to implant. The study was approved by the institutional review board and ethics committee, and all patients signed written informed consent prior to enrolment.

Echocardiography

All patients had a comprehensive preoperative echocardiographic assessment, and all echocardiographic studies were performed with a standard imaging system (Vivid E9, GE Medical, Horten, Norway) and software (Echopac BT12, GE Medical, Hortens, Norway) by experienced echocardiographers. Standard views and TDI data were collected and off-line analysis was performed on a PC workstation with the Echopac BT12 software. Standard echocardiography measures of left ventricular volumes were performed using the recommended Simpson's biplane method[13]. Mitral regurgitation (MR) severity was graded 0-3 according to the current guidelines [14]. Two experienced echocardiographers independently validated all data. Analysis of segmental radial strain was performed from parasternal views of the basal and mid LV segments, assessing peak radial strain derived from 2D speckle tracking data. Scanning depth was optimized, and scanning sector was set to allow for a frame rate between 70-90/s. Strain analysis was performed and analysed minimum of three times for every segment, and mean values were then used. Since radial speckle tracking strain analysis is difficult to perform with reliable reproducibility in the apical segments of the LV,

and there is good evidence that apical LV lead placement is unfavourable, the apical segments were not included in the analysis[15, 16].

Segments with very low strain values (<5% maximum positive strain) are usually not interpretable when it comes to determining the timing of contraction, since the curves then mainly oscillate around the zero-line with multiple small peaks. These segments are therefore not eligible as potential target segments for LV lead placement, at least not based on timing of mechanical contraction. Diagnostic problems mainly arise for segments with interpretable curves but low strain values either just below or above the proposed threshold value of 9.8% radial strain, where the differentiation between viable and non-viable myocardium is difficult. (see Fig. 1 and 2). Thus, for segments with radial strain values between 5-12%, the average strain values of neighbouring segments was calculated in an attempt to improve the diagnostic accuracy of the viability evaluation. Neighbouring segments were defined as any directly or diagonally adjacent segment in the mid- or basal part of the left ventricle (see Fig. 3), apical segments were left out due to unreliable strain curves. The relative difference between the target segment maximal strain and the neighbouring segments' averaged maximal strain was calculated and expressed in percent. The value, expressed in percent, was derived from *"(maximal positive systolic strain in the intended target segment) / (average value of maximal positive systolic strain in the immediately adjacent segments)",* thus representing a relative difference in maximal systolic strain in the intended target segment, as compared to neighbouring segments. For comparison with previously published studies[5, 6], an evaluation of presence of thinned myocardial wall (≤5mm) and pathologic acoustic appearance of the myocardium (qualitative; "yes" or "no") was made.

Cardiac magnetic resonance (CMR)

Data acquisition: A 1.5 T magnetic resonance imaging scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands) was used to acquire cine and late gadolinium enhancement (LGE) images during end-expiratory apnoea and ECG-gating. Parallel short-axis images were acquired covering the heart from base to apex as well as 4-chamber, 2-chamber and 3-chamber long axis images. LGE images were acquired approximately 10-15 minutes after intravenously administration of 0.2 mmol/kg gadolinium-based contrast agent (gadoteric acid, Gd-DOTA, Guerbet, Gothia Medical AB, Billdal, Sweden) with an inversion-recovery sequence. Inversion time was adjusted to null the signal from viable myocardium. Typical voxel size was 1.5 x 1.5 x 8 mm with slice gap of 0 mm. Typical image parameters were for cine: repetition time 2.8 ms, echo time 1.4 ms and flip angle 60˚, and were for LGE: repetition time 3.1 ms, echo time 1.6 ms and flip angle 15˚.

Data analysis: Segmental analysis of wall motion and viability of the left ventricle was performed according to the 17-segment model and according to established methods[17], [18, 19]. Wall motion of each segment was visually evaluated on a five-graded scale (0: hyperkinetic, 1: normokinetic, 2: hypokinetic, 3: akinetic, 4 dyskinetic). Viability of each segment was visually graded by the degree of transmural infarction or fibrosis (0: no infarction/fibrosis, 1: 1-25 % infarction/fibrosis, 2: 26-50 % infarction/fibrosis, 3: 51-75 % infarction/fibrosis and 4: 76-100 % infarction/fibrosis). Segments with transmural scar (>50% transmurality) were defined as non-suitable for LV lead placement, in accordance with previous studies [11, 20-22]. Total scar burden was calculated as the percentage of left ventricular myocardium with infarction divided by the total myocardium [10]. The results were presented in a standard 17-segment bull's-eye plot. Two experienced CMR physicians evaluated all the images and the result was only accepted when total agreement was reached.

Data integration from different modalities:

Standard 17 segment bullseye model was used as a reference for data integration, which is widely available in different imaging modalities. The CMR pictures were rotated to a position where the left ventricular segments were in identical position compared to the parasternal short-axis echocardiography views (Fig. 4). On the short axis slice representing the basal segments, the commissures of the mitral valve were used as reference points. At the mid segment level the papillary muscles were used as reference points. Care was taken to visualize the short axis views in exactly the same projection for echocardiography and CMR, and thereby the precise identification of the corresponding segments for the different imaging modalities was possible. The agreement of two experienced imaging specialists with competence in both echocardiography and CMR was required to identify the segments during the data integration.

Electrocardiography

All patients had QRS duration >120 ms. Left bundle branch block (LBBB) was defined as a broad, notched or slurred R-wave and absent q-waves in the lateral leads. Right bundle branch block (RBBB) was defined as an rSR' morphology in lead V1 or V2 and an S-wave greater than 40 ms or than the R-wave duration in lead I and V6. Left anterior hemiblock (LAH) was diagnosed if the electrical axis was -45° to -90° and there was a qR pattern in combination with RBBB. Left posterior hemiblock (LPH) was diagnosed if the electrical axis was 90° to 180° and there was an rS pattern in leads I and aVL or a qR pattern in lead III and aVF.

Statistical analyses

SPSS statistical software was used for all data analysis (IBM, SPSS ver: 21. 2012). Continuous variables are expressed as means (SD), categorical variables are presented as frequencies and percentages. Differences between groups were assessed using paired and unpaired Student t tests for continuous variables, Mann Whitney U test for variables with non-Gaussian distribution, and the Chi^2 test for categorical variables, or the Fisher's exact test for unordered categorical variables as appropriate. A two-sided p-value <0.05 was considered statistically significant. Intra-individual variability was expressed as the mean difference in percent between two readings. Inter-individual variability was avoided since two experienced physicians interpreted all echo-images simultaneously and agreement was reached in all cases.

Results:

Patients eligible for CRT therapy were consecutively included. Clinical characteristics are presented in Table 1 and the results from the standard echocardiographic measurements are available in Table 2. Echocardiographic evaluation was performed in all patients, and acceptable speckle tracking based radial strain analysis was possible in 404 of the total 408 evaluated mid- and basal left ventricular segments.

On average, maximal radial strain was 15.4±9.1 and time to peak strain was 486±149ms. There were no differences in maximal strain values between patients with ischemic or dilated CMP (15.3±7 vs. 15.6±11, p=n.s), or between men and women (15.1±8.3 vs. 16.7±9.9 p=0.09). In four cases there were two segments designated as equally good, based on the timing, but preference was then the given to the segment with the highest maximal positive strain.

Average strain values showed a correlation with both level of wall thickening and level of scarring / fibrosis; Segments with CMR-verified transmural (>50%) scar had lower strain values than segments without scar (10.5±3.6 vs 15.7±9.3, p=0.03). There was a strong correlation between level of wall thickening and strain values (p<0.001) (Fig. 5). However, in 67% of segments with transmural scar, radial strain values were above 9.8% indicating this as an eligible target segment for LV lead placement. Conversely, in 27% of segments with no scar or subendocardial scar <50%, strain values were below 9.8%, indicating them as non-suitable for LV lead placement. The sensitivity of strain <9.8% for identifying a segment with transmural infarction was only 33%, and the specificity was 73% (See table 3). In bivariate analysis, strain-values showed a significant correlation to wall motion (R=0.34, p<0.001) but a only a weak correlation to transmural scar (R=0.13, p=0.009). ROC analysis of strain for prediction of transmural scar showed an area under curve of only 0.70 (p=0.01). A total of 19 segments had strain values <9.8, myocardial wall thickness ≤5mm and pathologic acoustic appearance; of these 37% (n=7) segments had viable myocardium, 53% (n=10) had subendocardial infarction and 11% (n=2) had transmural infarction. Conversely, of all segments with verified transmural infarction, only 13% had a combination of strain-values <9.8%, wall thickness ≤5mm and pathologic acoustic appearance.

When comparing the average difference in maximal strain between target segment and neighbouring segments (Fig. 3), the difference was significantly lower in viable segments (i.e. with hypokinesia but no scar), than in target segments with scar/fibrosis; 35% vs. 64%, p=0.047. In segments with transmural infarction (i.e. 50-100% transmurality), the difference was even more pronounced with an average difference of 87% between target segment and neighbouring segments compared to 38% for non-transmural and viable segments (p=0.03).

On average, for patients with ischemic cardiomyopathy, 9% of segments were defined as non-suitable because of transmural scar, and for non-ischemic etiology the corresponding number was 2%. Total left ventricular scar burden was higher for ischemic patients compared to non-ischemic patients (16±25% vs. 5±16 % respectively, $p< 0.0001$), and mainly non-transmural scar was detected in the group with dilated cardiomyopathy. In 33% of cases, there was some degree of scar in the target segment with latest mechanical delay, and these patients generally had ischemic cardiomyopathy (78%), as well as the one patient where echocardiography indicated a segment with transmural scar as suitable target segment. Intraobserver variability for strain measurements was 7.1 % and readings did not differ significantly ($p=0.12$).

Discussion:

This prospective study confirms that for patients with heart failure eligible for CRT, there is a strong correlation between maximal speckle tracking radial strain values and hypokinesia and scar tissue on cardiac magnetic resonance (CMR) investigation. Segments without scar and normal wall thickening generally show higher maximum radial strain values. However there is considerable variation in the absolute values and in many cases the maximal strain value alone is not sufficient to rule out a non-suitable segment for LV lead placement. We show that by looking at the relative difference in strain values compared to neighbouring segments of the left ventricle, the diagnostic accuracy is improved when it comes to differentiating between transmural scar and viable myocardium. However, since the patient-to-patient variation was quite large in our study, we have not proposed an optimal cut-off value for relative difference in strain - and until further validation, these data should be interpreted with caution. Nevertheless, a large difference in percent versus neighbouring segments implies a scar in the evaluated segment with low strain values, and taken together with other data such

as qualitative evaluation of myocardial thinning and echogenicity, this may help the differentiation between viable / non-viable segments.

Determining segmental viability in a reliable way is important, in order to avoid placing the LV lead in cardiac segments with transmural scar tissue, which has been shown to have a negative prognostic value[23-25]. It is likewise important to discriminate between non-viable myocardial tissue and viable tissue with hypokinesia or akinesia, since available evidence does not suggest any harm when pacing in proximity to akinetic (but viable) segments, and these segments could be mistakenly deferred for LV lead placement on the basis of strain values below 10%[26]. Thus, if segments with transmural scar are not sufficiently differentiated from non-scarred segments, there is a risk of placing the LV lead in a suboptimal place even though mechanical dyssynchrony evaluation shows a late activation. The fact that a scarred segment will be moved passively only by "pulling" from an adjacent viable segment, and thereby by definition will be moving *after* the pulling segment, increases the risk of designating it as the optimal segment with maximum mechanical delay. In our small series there were four cases where the latest segment was not chosen to be the optimal segment, either due to strain values <9.8% or due to the segment being in the septum and therefore not interesting for an LV lead implant. This may reflect that these patients did not have a proper LBBB on ECG and / or prior myocardial infarction with scarring of the left ventricle; hence the mechanical activation pattern was different.

Cardiac MR is expensive and although more and more available, it is still resource demanding. Echocardiography on the other hand has the advantage of being less expensive and available bedside in all cardiology departments, and if a combination of traditional 2D imaging and additional speckle tracking analysis could suffice for a comprehensive

preoperative evaluation regarding target segments, this would likely save resources and be cost-efficient. However, in order to be clinically useful and potentially obviate the need for CMR, speckle-tracking data need to be reproducible and reliable in identifying segments without myocardial scar and late segmental mechanical timing in the left ventricle. Both the TARGET study and the recently published STARTER study used strain analysis based on 2D echocardiography parasternal radial strain to guide CRT lead placement in the left ventricle, and showed similar positive short-term results[5, 6]. Khan et al. chose to have a cut-off of 9.8% radial strain as a minimum for a selected target segment, based on previous work showing less beneficial effects of low amplitude strain segments[27]. Saba et al. made a composite evaluation and excluded potential target segments if strain values were "low" and there was visual evidence of transmural infarction (i.e. thin myocardial wall with different echogenicity). Even though there are no data regarding if the chosen target segments indeed had transmural or non-transmural infarction, the results were impressive with a significant increase in responders in both studies, supporting the use of radial strain as a selection tool for LV target segments. ~~Adding the differentiation technique for viability proposed in our study may possibly improve the results even further in the future.~~

Judging from our data, the greatest difficulties in selection of an appropriate target segment arise in patients with ischemic cardiomyopathy. None of the three discussed strain-based methods (i.e. our proposed method and the two methods used by Saba and Khan respectively) was optimal for selection of suitable target segments *without* transmural scar in this patient cohort. Cardiac MR adds more information in ischemic patients than in patients with dilated cardiomyopathy, since in the latter group transmural scar is unusual, and the addition of data from preoperative CMR is therefore unlikely to change the target segment. However, differentiation between DCM and ICMP is not always clear-cut, unless the patient has done a CMR. Areas of fibrosis and infarction can be present in a patchy or localised pattern in

patients presumed to have a DCM. Even after CMR, the precise diagnosis is sometimes unclear, and coronary angiogram or stress-evaluation may be needed to confirm the genesis of areas with late gadolinium enhancement. This highlights the need for "an open mind" for the possibility of scarred segments, regardless of the presumed ethiology of heart failure, and supports a thorough evaluation by 2D speckle tracking radial strain. In cases with ambiguous results, and in particular for those patients with ischemic cardiomyopathy, adding information from CMR may be crucial. If CMR is not available for scar evaluation, using speckle tracking data on relative differences in strain values of the target segment compared to surrounding segments (in addition to evaluation of myocardial thickness and echogenicity) may be beneficial. Whether this approach transforms into more responders to CRT has to be investigated in future prospective trials.

Limitations

The major limitation is the small number of patients included in the study, which means that the results will have to be confirmed by other groups as well. However, the patients were recruited prospectively and clinical data are representative of the published larger CRT trials, so the results are likely to be valid in this group of patients. Speckle tracking is difficult to perform for untrained echocardiographers, and results will be less reliable in inexperienced centres. The technique is under development, and the different vendors of ultrasound machines are introducing more and more automatic functions for these kinds of analyses, which is likely to improve the learning curve in the future. Even though the comparison of absolute difference in strain values differed significantly between target segments with scar versus segments with no scar, there was an overlap between the groups, and further studies need to establish a the proper cut-off value in order to optimize the clinical usefulness of this tool.

Conclusion:

Speckle tracking radial strain is useful for assessment of mechanical delay and viability in CRT recipients, but ideally the preoperative evaluation should include CMR in patients with ischemic cardiomyopathy. By using 2D speckle tracking strain and combining it with evaluation of relative differences between segmental strain values, potential target segments with low strain values can be more reliably classified as viable / non-viable. This may help in guiding the optimal LV lead position in cardiac resynchronization therapy.

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List of abbreviations

CRT	Cardiac resynchronization therapy
CMR	Cardiac Magnetic Resonance
LBBB	Left Bundle Branch Block
RBBB	Right Bundle Branch Block
ECG	Electrocardiogram
TARGET	Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy
STARTER	Speckle Tracking Assisted Resynchronization Therapy for Electrode Region Trial
LV	Left ventricle
DCM	Dilated Cardiomyopathy
ICMP	Ischemic cardiomyopathy
2D	Two-dimensional (echocardiography)
TDI	Tissue Doppler imaging

Figure legends:

Figure 1. Example of a patient with dilated cardiomyopathy. In the upper half of the picture data from the basal segments is shown, and in the lower part data from the mid segments is shown. The short axis views of the left ventricle (LV) with echocardiography are shown to the left; with the upper picture showing the segment division and the lower showing the colorkinesis and values of the strain assessment. In the middle the segmental strain curves and values are shown. The right pictures show the corresponding LGE sequence from CMR. The CMR with LGE sequences shows no scar in the examined segments. The results from the strain analysis generally show low amplitudes. The latest segment in this case is the mid inferior (blue) although the strain value is only 8.26. However, since all segments have low amplitudes, the relative difference from neighbouring segments in this case was only 9.3%. The typical early septal activation (septal flash) is also represented on this figure.

Figure 2. Example of a patient with ischaemic cardiomyopathy (similar recordings as in fig. 2). In this case the CMR with LGE shows transmural scar in segment 3 and segment 4 (basal septal and basal inferior). In the septal segment (red arrow and segment) the strain value suggests non viable myocardium which is correct. On the other hand the strain value of the inferior segment (blue arrow and segment) is 10, suggesting that the examined segment is viable but in fact there is a transmural scar. The maximal strain values for the neighbouoring segments are generally higher, thus the relative difference to the target segment in this case was 65%.

Figure 3. A schematic picture from the left ventricle divided into 17 segments. The white arrow is pointing to a target segment (red) with strain value between 5 - 12%. The yellow marked segments are considered as adjacent segments (either directly or diagonally).

Maximal strain values from these segments are averaged and the value is compared to that of the target segment, yielding a relative difference.

Figure 4. Corresponding images showing the alignment of the respective segments on echocardiography (left side) and CMR (right side). The arrows are pointing to the papillary muscles at the mid left ventricular level

Figure 5. Maximal strain values (averaged) in segments with varying degrees of hypokinesia, stratified by simultaneous presence of scar.

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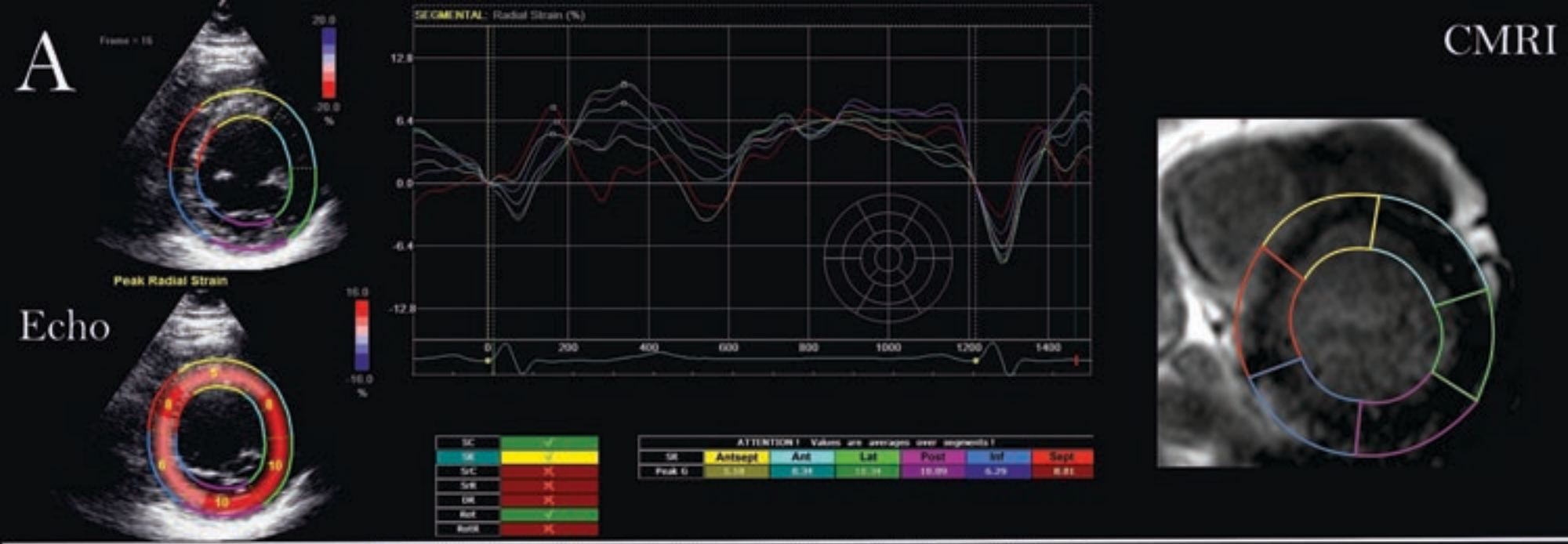
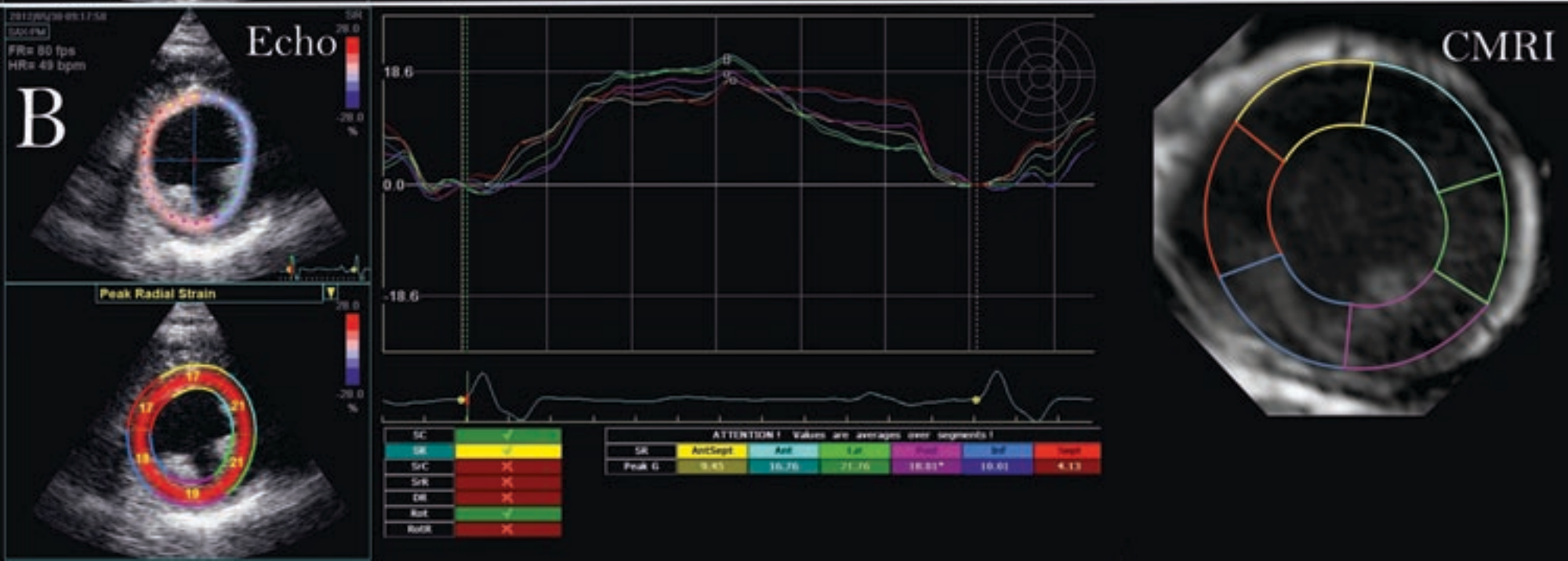
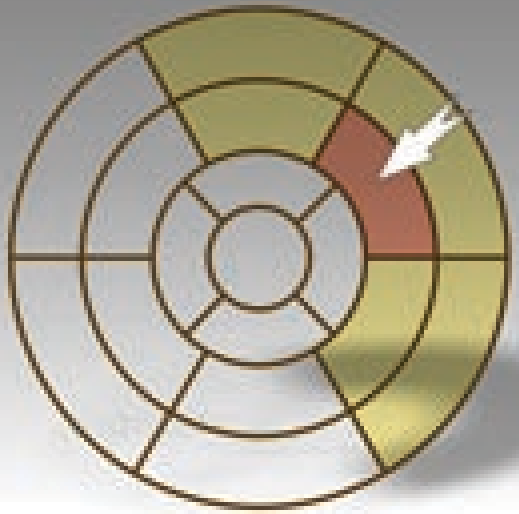

A
Peak Radial Strain
Echo
SEGMENTAL: Radial Strain (%)
CMRI
ATTENTION ! Values are averages over segments !
Antsept
Ant
Lat
Post
Inf
Sept

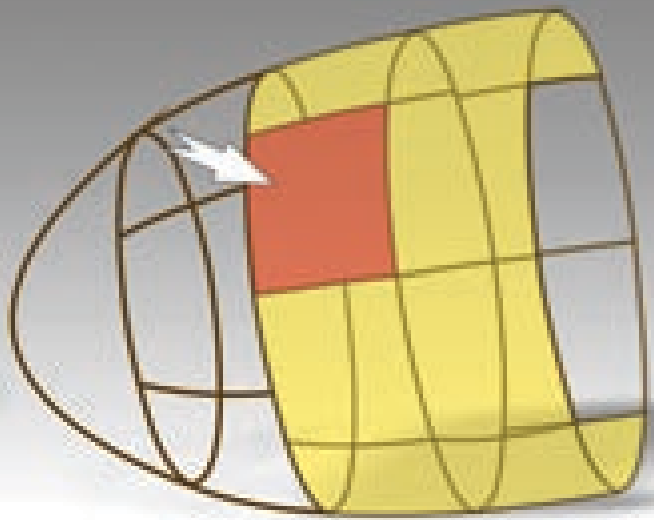

B
Peak Radial Strain
Echo
SEGMENTAL: Radial Strain (%)
CMRI
ATTENTION ! Values are averages over segments !
Antsept
Ant
Lat
Post
Inf
Sept

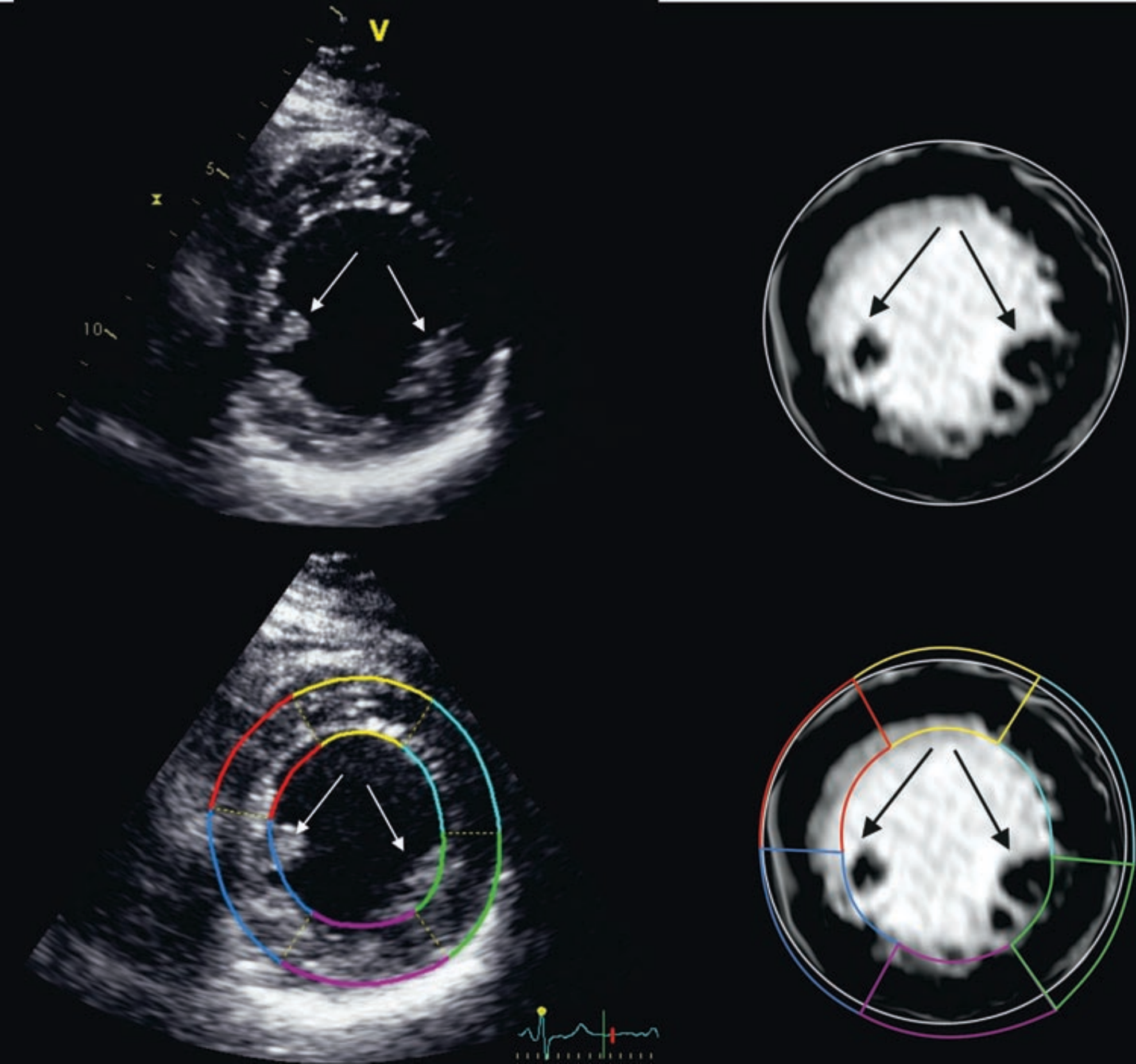

Echo
A
FR= 80 fps
HR= 50 bpm
Peak Radial Strain
18.6
0.0
-18.6
CMRI
ATTENTION ! Values are averages over segments !
SR
Peak G
AntSept
Ant
Lat
Inf
Sept
9.45
16.76
21.76
10.01
4.13

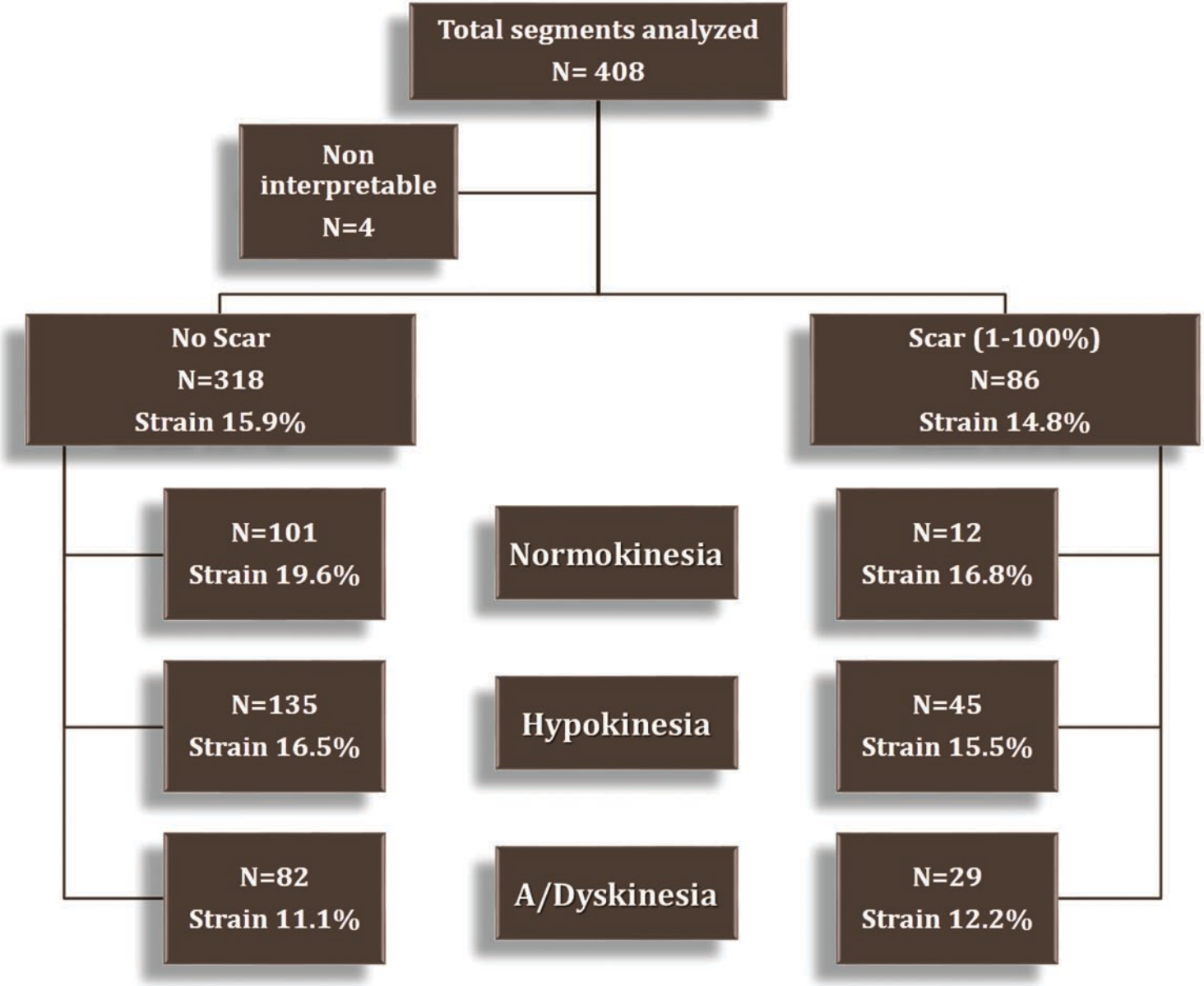

Echo
B
FR= 80 fps
HR= 49 bpm
Peak Radial Strain
18.6
0.0
-18.6
CMRI
ATTENTION ! Values are averages over segments !
SR
Peak G
AntSept
Ant
Lat
Inf
Sept
9.45
16.76
21.76
10.01
4.13

1. Basal Anterior
2. Basal Anteroseptal
3. Basal Inferoseptal
4. Basal Inferior
5. Basal inferolateral
6. Basal anterolateral
7. Mid Anterior
8. Mid Anteroseptal
9. Mid Inferoseptal
10. Mid Inferior
11. Mid inferolateral
12. Mid anterolateral






V
5
10


Total segments analyzed
N= 408
Non interpretable
N=4
No Scar
N=318
Strain 15.9%
Scar (1-100%)
N=86
Strain 14.8%
N=101
Strain 19.6%
Normokinesia
N=12
Strain 16.8%
N=135
Strain 16.5%
Hypokinesia
N=45
Strain 15.5%
N=82
Strain 11.1%
A/Dyskinesia
N=29
Strain 12.2%