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Segmental myocardial strain in myocarditis in young adults: Natural variability versus myocarditis signal

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Abstract

Introduction: Myocardial segmental peak strain (pkS) is used in detection and characterization of myocarditis; however, its clinical diagnostic values are inconclusive. To reveal potential causes of positive and negative study results and evaluate the diagnostic potential of pkS, we quantified its natural variability and compared it to the change in pkS caused by myocarditis.

Methods: The study included 34 patients (sex: 29 M, age: 30 ± 7.5 years) with diagnosed myocarditis which underwent two-dimensional speckle tracking echocardiography (2D-STE) in three apical echocardiographic planes at the time of diagnosis (M0) and 6 months (M6) following treatment. In total, 18 longitudinal segmental strain patterns were extracted at each session and a pkS was found as a minimum strain value during systole. The average natural variability ($\overline{NVm}$) was calculated from sector values of all unique pkS absolute differences separately at M0 and M6, and myocarditis signal ($\overline{MC}$) was calculated from pkS difference in the same patient between M6 and M0. A signal-to-noise ratio was calculated as ($\overline{MC}/\overline{NV(M6)}$).

Results: We found that the average pkS at M0 and M6 were different (−19% ± 5% and −20% ± 5%, $p < 0.05$), and the difference was largest around the basal-posterior segment. There was no difference in ($\overline{NV}$) between M0 and M6 (5.1% ± 4.2% and 5.0% ± 4.2%, $p > 0.05$), but they were both significantly larger than ($\overline{MC}$) (−1.3% ± 5.3%, $p < 0.05$). The average signal-to-noise ratio was 0.3, and it was largest in the basal-lateral region and lowest in the anterior-septal region.

Conclusion: We found that natural variability in pkS is significantly larger than the change of pkS due to myocarditis. Thus, information about inflammation severity and location from pkS alone needs further investigation.

KEYWORDS

heart, myocarditis, natural variability, segmental strain, speckle tracking echocardiography

1 | INTRODUCTION

Myocarditis is an inflammatory condition of the myocardium that can lead to significant cardiac dysfunction and structural abnormalities.[1–3] The gold standard for noninvasive diagnosis confirmation is cardiac magnetic resonance (CMR) in combination with late gadolinium enhancement. A recent alternative is two-dimensional speckle tracking echocardiography (2D-STE) myocardial deformation measurement, which may simplify diagnosis confirmation and bring it to the ambulatory setting.[4,5] When diagnosing myocarditis, the most significant clinical changes were found in the global longitudinal peak strain (pkS).[6,7] Contrary to global pkS, segmental pkS values represent the mechanics of the local myocardium and differ with respect to its position in the left ventricle.[8] The segmental pkS bears the potential to provide insights into local myocardial tissue properties; for example, in myocarditis they could reveal the extent and location of the inflammation.[6] The prognostic value of segmental pkS, however, has not been confirmed in all studies. Unlike global pkS, which holds predictive value, segmental pkS does not necessarily possess such characteristics.

Uppu et al. observed that 2D-STE segmental longitudinal pkS was decreased in segments with late gadolinium enhancement detected by CMR.[9] Their work signified that 2D-STE pkS can be a useful noninvasive tool for diagnosing and prognosticating acute myocarditis, especially when combined with LGE and troponin levels. Amzulescu et al. compared 2D-STE with two-dimensional tagged CMR imaging (2D-Tagg) myocardial strain measurement.[10] Their findings showed that global pkS measurements with 2D-STE agreed well with 2D-Tagg, but that there was higher variability and lower accuracy at a segmental level, suggesting that 2D-STE may be less reliable and less accurate for assessing segmental pkS compared to global measurements. Inter-vendor agreement of global and segmental longitudinal strain using vendor-specific software was analyzed by Shiino et al. after standardization initiatives.[11] The results showed excellent correlation and similar global longitudinal pkS measurements between vendors. However, wide limits of agreement persisted for segmental pkS measurements, emphasizing the importance of considering variability when using vendor-specific software for serial measurements.

Although many studies have showcased the effectiveness of 2D-STE in evaluating myocardial strain irregularities in myocarditis,[6,7] doubt persists regarding segmental pkS applicability in myocarditis evaluation.[12] The primary concern revolves around the inherent heterogeneity of myocardial pkS.[10] This heterogeneity can be influenced by factors of pathology such as the extent and location of myocardial inflammation,[4] the severity of myocardial injury, and individual natural variations in cardiac anatomy and function.

This study explores the alteration in segmental pkS caused by myocarditis and compares it with natural physiological variability. By studying segmental pkS values in patients at the time of diagnosis and 6 months later following treatment, we sought to differentiate the pkS component associated with myocarditis from those attributable to natural physiological variability.

2 | METHODS

We retrospectively studied patients treated for acute myocarditis from January 2017 to October 2020. The diagnosis of suspected acute myocarditis was established according to clinical presentation, increased troponin I levels, "myocarditis-like" MRI findings, and excluded coronary artery disease by coronary angiography.[13] The patients were treated with ACE inhibitors and beta blockers to optimize cardiac remodeling and prevent cardiac arrhythmias. Some of the patients also received immunomodulatory treatment with intravenous immunoglobulins (IVIG). At 6-month follow-up (M6), all patients were asymptomatic. Echocardiography showed normal left ventricular ejection fraction (LVEF) (>52), and troponin levels were negative. The study was conducted in accordance with ethics committee requirements for retrospective analysis of anonymized clinical images. The study was approved by the local ethics committee (resolution no. 0120-37/2017/4 on November 27, 2017).

An experienced cardiologist recorded transthoracic echocardiogram at the acute phase of myocarditis (M0) and at 6-month follow-up (M6). Transthoracic echocardiography (GE Vivid E95) was recorded sequentially in three apical views (four-chamber view, two-chamber view, and three-chamber view) at a frame rate of 60–80 frames/s. All the images were ECG gated. Aortic valve closure and opening times were determined from continuous-wave Doppler.

Speckle-tracking analysis was performed offline by the same cardiologist using EchoPAC software (version 206, GE Healthcare, USA) and application Q-analysis. The endocardial border of the ventricle was manually traced (8–10 points) over one frame. The result of the speckle-tracking analysis of a recording of each plane was six longitudinal strain patterns: strain values over time as demonstrated in Figure 1. They corresponded to apex, mid-ventricle, and base location, respectively, for the anterior and posterior wall. Strain measurements were then obtained from all the planes in 18 sectors distributed longitudinally across the left ventricular wall, covering every region. The reference value of strain was calculated at end diastole which was determined from the aortic valve opening and the ECG-R wave.

The strain values in time (strain trace) were exported from EchoPAC software into MATLAB (MathWorks R2022) where they were further processed as signals. The acquisition frame rate and the heart rate differed between the recordings of the planes on the same subject. Thus, the strains were resampled to the mean heart rate of the subject and to a frame rate of 100 frames/s. Moreover, the strain patterns were refined by removing outliers. Any strain pattern that deviated, on average, by more than three standard deviations from the subject's mean strain pattern throughout the entire cycle was replaced with the subject's average strain pattern.

The strain pattern from each sector was processed to find pkS as a minimum strain value during the cardiac cycle. Global strain was calculated as an average value of strain across the entire myocardium. Natural variability (NV) was determined as the difference in pkS among the subjects in each sector. For example, in sector $s = 1$ at time $m = \mathrm{M0}$, all differences in pkS between subjects were calculated and averaged. This result represents the natural variability detected in

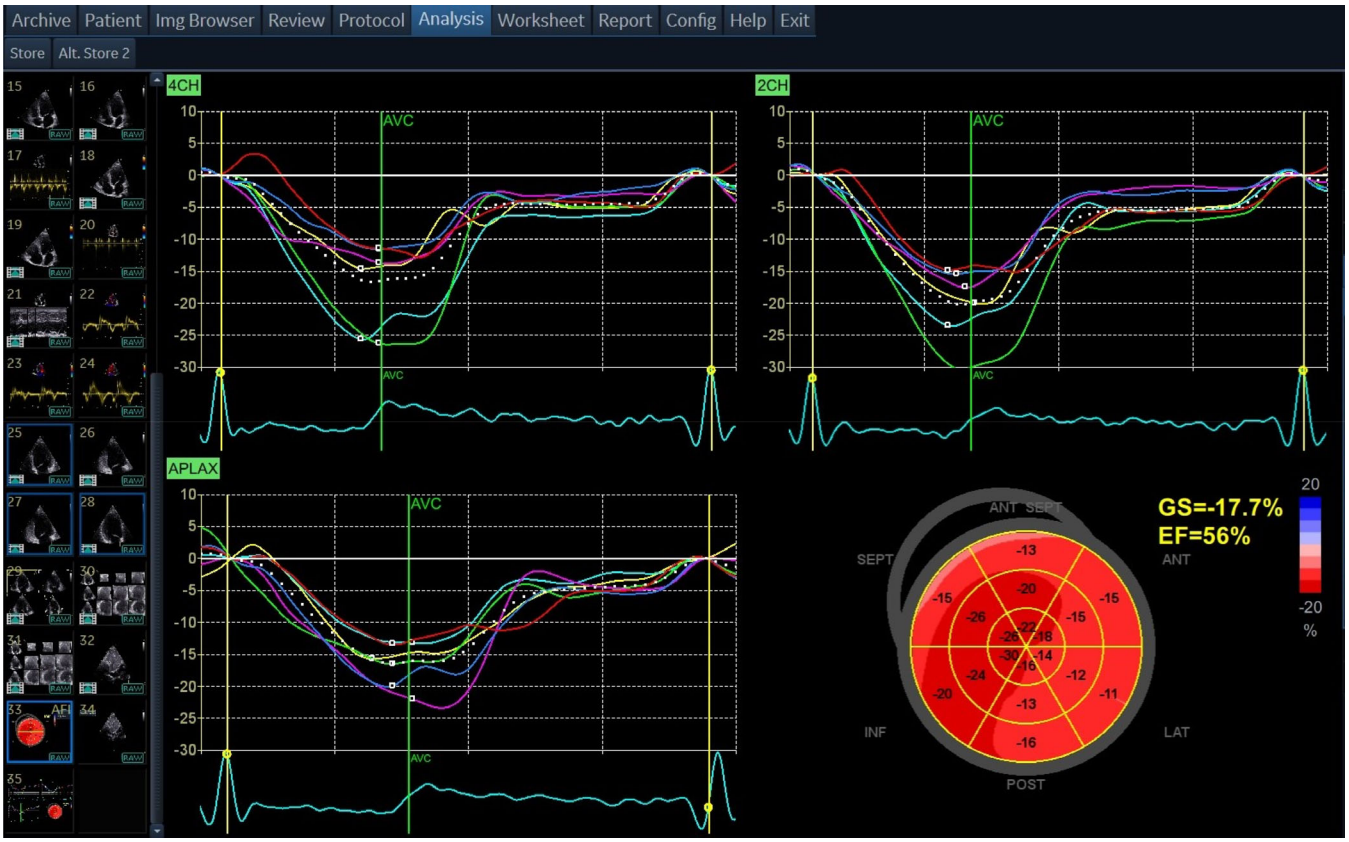

FIGURE 1 Strain curves over time in three projections 4CH, 2CH and APLAX were obtained from cine echocardiographic image of left ventricle using EchoPAC software. Right-bottom: peak strain values for all regions shown in bulls eye plot.

sector 1 at the time of myocarditis diagnosis ($\overline{NV_{s=1,m=M0}}$). The equations which we used are:

$$NVs,ij,m = \left|pkS_{s,i,m} - pkS_{s,j,m}\right|$$

where *s* stands for sector, *i* and *j* generate all combinations of two different subjects (strictly upper triangular matrices), and *m* stands for measurement at time M0 and time M6. Then averages of NVs, *ij*, and *m* values in all sectors at M0 or M6 ($\overline{NVm}$) and in each sector ($\overline{NVsm}$) were calculated, respectively.

The myocarditis signal (MC) was determined as the difference in pkS obtained from the same subject at time M0 and at time M6 in each sector separately:

$$MCs,i = pkS_{s,i,m=M6} - pkS_{s,i,m=M0}$$

where *s* stands for sectors, *i* for subjects, and *m* for measurements at time M0 and time M6. The average myocarditis signal was calculated as the average of MCs, *i* ($\overline{MC}$) and average segmental myocarditis signal as the average of all MCs, *i* in sector *s* ($\overline{MCs}$). The signal-to-noise ratio of each sector was calculated as the ratio between the average $\overline{MCs}$ and average $\overline{NVsm}$ at $m = M6$. M6 was selected because we wanted to determine what is normal "background noise," which we can only obtain from measurements on healthy subjects.

TABLE 1 Summary of patient characteristics.

No. of cases (*n*)	34
Age (years)	30 ± 7.6
Gender (M/F)	29/5
BMI (kg/m^2)	26 ± 5
HR (bpm)	66 ± 10
Max. Troponin (ng/mL)	21 ± 28
CRP elevated (ng/L)	62 ± 61
EF (%)	63 ± 9
GLS (%)	−19 ± 5
LGE extent (%)	24 ± 5

Abbreviations: BMI, body mass index; CRP, C-reactive protein; EF, ejection fraction; GLS, global longitudinal strain; HR, heart rate; LGE, late gadolinium enhancement.

2.1 | Statistics

Results are reported as average ± standard deviation percentile value. $\overline{NVm}$ and $\overline{NVsm}$ values were compared between measurements at M0 and M6 with a paired *t*-test. $\overline{NVm}$ for $m = M0$ and $\overline{MC}$ values were compared with an unpaired *t*-test. *t*-test significance was accepted when $p < .05$. Normal distribution of samples was tested with Kolmogorov–Smirnov test.

3 | RESULTS

The study included 34 patients with myocarditis. Their baseline characteristics and echocardiographic parameters are shown in Table 1. On admission, median troponin I level was 12,755 ng/L (max 146,000 ng/L, min 129 ng/L, normal <34 ng/L), and median C-reactive protein level was 35.5 mg/L (max 260 ng/L, min <5 ng/L). At M6 all patients were asymptomatic, and troponin levels and inflammatory parameters were negative.

The mean heart rate for all subjects was the same at M0 and M6. The mean framerate of echographic images acquisition was 65 ± 10 and 68 ± 5 fps at M0 and M6, respectively. Figure 2 shows measured strain patterns for one subject during an almost complete cardiac cycle. At end diastole, the strain values are all zero and they generally decrease until they reach the pkS (black dot).

The average global pkS for all subjects is −19 ± 5% and −20 ± 5% for M0 and M6 measurements, respectively. The difference is significant (paired *t*-test, $p < .05$). The results of the average segmental pkS for all subjects for M0 and M6 are shown in Figure 3. The difference between M0 and M6 is not significant in all sectors, but only in marked sectors (*) around the basal posterior segment. Segmental pkS

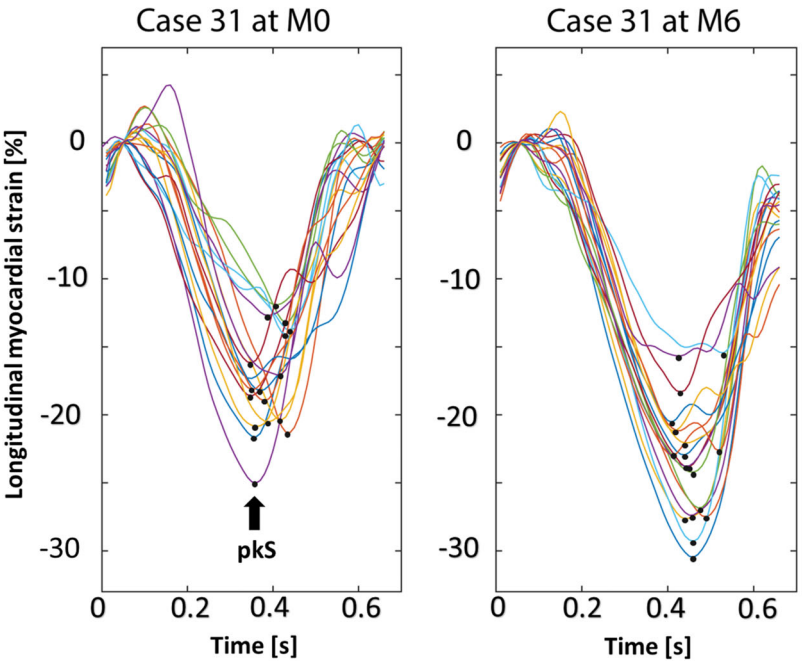

FIGURE 2 Strain pattern curves for all 18 sectors of subject no. 31 at the time of diagnosis (left, M0) and 6 months after the diagnosis, when the subject was cured (right, M6). Peak strain (pkS) in each strain curve is marked by a black dot.

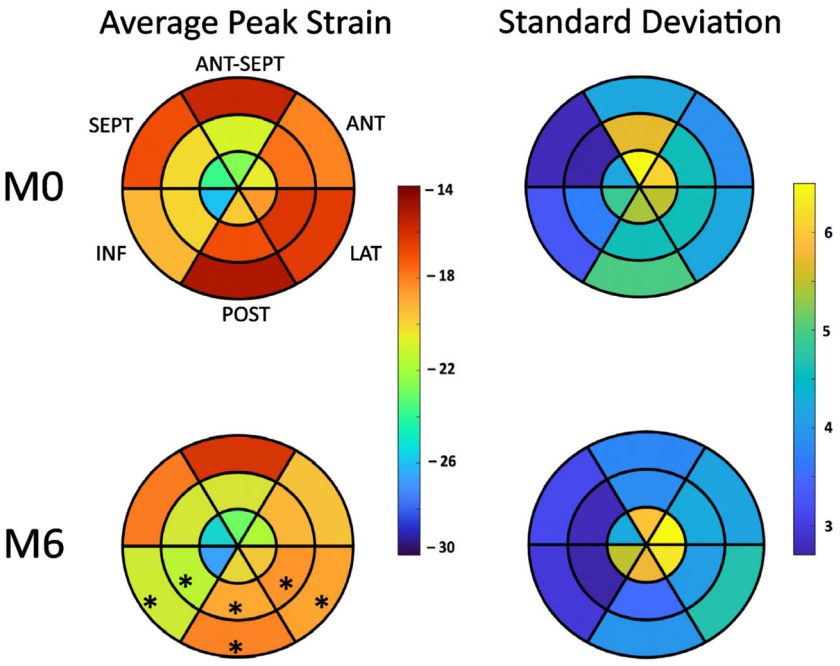

FIGURE 3 Average peak strain in each sector (left) and its standard deviation (right) for all 34 patients at the time of diagnosis (M0) and 6 months after the diagnosis, when the subject was cured (M6). Significant change in peak strain at M6 with respect to M0 is marked with (*). Note that peak strain is highest in apex, where one can also observe the largest standard deviations between patients. The segments are named according to their location: Anterior–Septal (ANT–SEPT), Anterior (ANT), Septal (SEPT), Lateral (LAT), Posterior (POST), Inferior (INF).

is on average highest in the apical region, and its standard deviations (Figure 3, right) are correspondingly highest.

The average values of NV and MC are shown in Table 2. We found that $\overline{MC}$ is significantly lower than $\overline{NVm}$ for both $m = $M0 and $m = $M6. The average signal-to-noise ratio for all sectors is 0.3.

Figure 4 shows the average segmental values of NV, MC, and signal-to-noise ratio. The lowest $\overline{NVsm}$ (Figure 4A,B) is found in the septal and inferior direction for both M0 and M6. Generally, the apex shows more variability than the midventricular and basal regions. The most negative values of $\overline{MCs}$ (Figure 4C) are in the postero-lateral direction in the basal and mid-ventricular regions. Figure 4D shows that the signal-to-noise ratio is largest in the postero-lateral direction in the basal region.

4 | DISCUSSION

We studied segmental pkS in a group of patients with myocarditis at diagnosis and 6 months later after completion of the treatment. We estimated the NV of pkS (5.1%) and compared it to the change in pkS due to myocarditis (1.3%). We found that the NV is on average three times larger than the change due to myocarditis. With respect to the location in the left ventricular wall, it ranges from two times in the basal–lateral region to 10 times in the anterior–septal region. We furthermore found that global strain is significantly more negative after the treatment and, with respect to the segmental pkS, we found significantly more negative values in six basal-posterior–oriented segments, which corresponds well with previously published studies.[14,15]

To put our findings in perspective, we can compare them with previously reported variabilities in global and segmental pkS. GLS has shown high inter and intra observer reproducibility with the correlation coefficients and intraclass correlation coefficients ≥0.95, variability in repeated GLS measurements range from ±2% to ±5%.[14] Regarding segmental pkS, Farsalinos et al. reported intra- and interobserver variability of up to 1.7%[15] and Wang et al. confirmed similar findings.[16] Moreover, studies of inter-vendor agreement on segmental longitudinal pkS revealed the variability ranging from 4.5% by Mirea et al.[17] to 16.2% by Shino et al. in 2016.[11] We can conclude that NV is considerably larger than intra and interobserver variability in segmental pkS and that myocarditis signal is small with respect to other measurement variabilities.

The estimation of the segmental signal-to-noise ratio is our novel contribution. It is important because segmental pkS is considered a rich information source on ventricular mechanics. Substantial effort has been invested into extracting segmental distribution of myocardial tissue properties from segmental pkS.[16,17] The analyses could provide insights into the specific changes in myocardial strain induced by the inflammatory process in myocarditis. Understanding the alteration in segmental pkS caused by myocarditis is important for several reasons. First, it can aid in the early diagnosis and monitoring of myocarditis because myocardial strain analysis has the potential to detect subtle changes in myocardial function even before the onset of symptoms or

TABLE 2 Natural variability and myocardial signal.

Variable	Value (%)
$\overline{NVm}$, $m = $M0	5.1 ± 4.2
$\overline{NVm}$, $m = $M6	5.0 ± 4.2
$\overline{MC}$[a]	−1.3 ± 5.3

[a]Statistically significant difference between MC and NV at times M0 and M6; the difference between $\overline{NVm}$ at M0 and M6 was not significant.

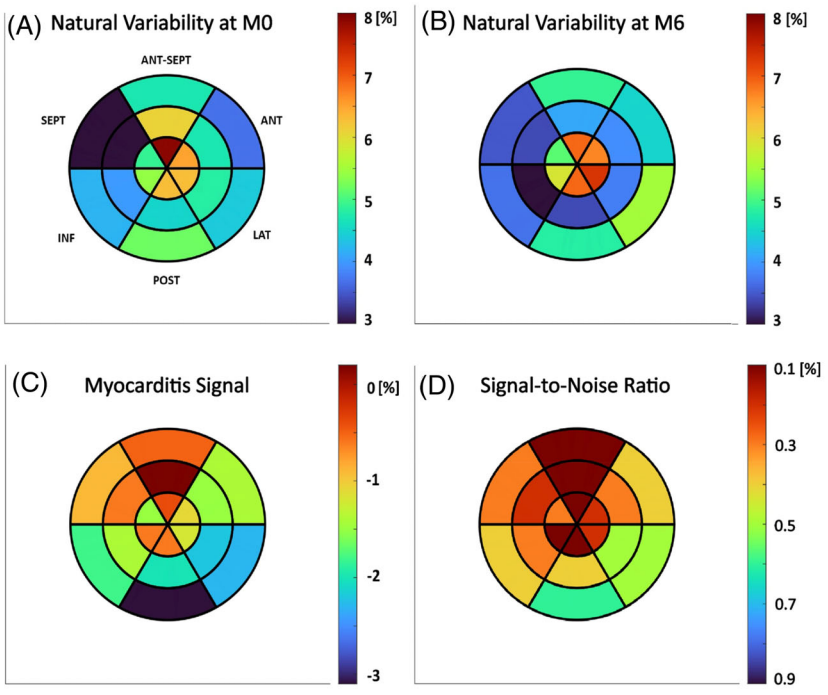

FIGURE 4 Average segmental natural variability $\overline{NVsm}$ at M0 (A) and M6 (B), myocarditis signal $\overline{MCs}$ (C), and signal-to-noise ratio (D). The segments are named according to their location: Anterior–Septal (ANT–SEPT), Anterior (ANT), Septal (SEPT), Lateral (LAT), Posterior (POST), Inferior (INF).

detectable changes in traditional cardiac parameters. Additionally, studying the natural variability of segmental pkS within the population can provide a context for interpreting strain measurements and establishing reference values for different age groups, potentially enhancing the diagnostic accuracy of myocarditis evaluation using strain analysis. However, a few studies have shown no solid case for segmental pkS.[10] Our study showed that the reason why it is so difficult to extract meaningful data from a measurement on one individual is large natural variability in pkS. It seems as if the differences in how different hearts mechanically contract are large in comparison to the change in cardiac mechanics induced by myocarditis.

Our study used a segmental pkS as the main indicator of segmental myocardial mechanics. The pkS is a standard parameter in the clinic; however, it is only one time-point in the strain pattern curve. It is likely that the change of the myocardial segmental mechanics manifests in at least two parameters: pkS and the time when this peak is achieved. In the future, pkS, its position in time, and other strain pattern curve features should be used to evaluate the change in segmental myocardial performance.

4.1 | Study limitations

The main limitation is that it is a single center study with a relatively small sample size that could result in reduced power of any statistical findings. Moreover, our study involves retrospective analysis of the data acquired by the same operator and the measurement system resulting in the lack of intra and inter operator variability due to which reliability of the findings could only be compared to published values. Further studies are needed for the validation of our findings. Echocardiographic recordings were processed with EchoPAC Q analysis version rather than AFI, and manual delineation of the endocardial borders could introduce inconsistencies in regional strain values. Additionally, different vendors have proprietary methods for acquiring global strain, which are not publicly disclosed, potentially leading to variability in GLS measurements. Other limitations of our study include study group heterogeneity in the percentage of myocardium affected and the spatial distribution of the regions affected. Due to limited resources, we were unable to get the strain data of healthy controls from the same operator and device. To overcome this limitation, the subjects at time M6, when they were cured, were considered as controls, but they might still have some residual inflammation that is undetectable by regular clinical tests. When observing the segmental distribution of pkS and $\overline{NVsm}$, we can see that larger variability is present in apical regions, which is likely due to imperfect echocardiographic recordings, tissue delineations, and ventricle curvature.

5 | CONCLUSION

Segmental myocardial strains are potentially a rich source of data on cardiac mechanics that are readily available in a cardiology ambulatory setup, but which are not utilized at present. Only the global pkS shows a clinical diagnostic significance, but all information on the spatiotemporal distribution of mechanical properties is lost in it. Our study found that natural variability in segmental pkS is significantly larger than the change in pkS due to myocarditis. This finding means that it is difficult to obtain spatiotemporal information about the severity and distribution of myocarditis from segmental pkS for an individual. Perhaps the analysis of a complete segmental strain pattern curve instead of a single point could reveal additional information.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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