

Original Research

Value of Apical Circumferential Strain in the Early Post-Myocardial Infarction Period for Prediction of Left Ventricular Remodeling

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Key words:

Speckle tracking echocardiography, deformation, strain.

Background: Left ventricular (LV) remodeling after acute myocardial infarction (AMI) is related to increased morbidity and mortality. The aim of the present study was to examine whether LV deformational and torsional parameters can predict LV remodeling in patients with AMI.

Methods: Forty-two patients (age 57 ± 14 years) presenting with an anterior ST-elevation AMI and treated with primary percutaneous transluminal coronary angioplasty (PTCA) were included in the study. Four days post MI, LV ejection fraction (EF), LV torsion, longitudinal (4-, 3- & 2-chamber) and circumferential strain of the LV apex were evaluated by conventional and speckle-tracking echocardiography. The echocardiographic study was repeated at 3 months post-AMI and patients with LV remodeling, i.e. an increase $>15\%$ in LV end-systolic volume (LVESV), were identified.

Results: The 13 patients with LV remodeling had significantly more impaired apical circumferential strain ($-7.3 \pm 2.2\%$ vs. $-18.9 \pm 5.2\%$, $p=0.001$), EF ($42 \pm 7\%$ vs. $48.9 \pm 6\%$, $p=0.005$), LV apical rotation ($6.8 \pm 4.8^\circ$ vs. $11.1 \pm 4.0^\circ$, $p=0.027$), and LV global longitudinal strain ($-9.7 \pm 1.9\%$ vs. $-12.9 \pm 2.9\%$, $p=0.03$) on the 4th day post-AMI, in comparison to those without LV remodeling. Apical circumferential strain on the 4th day post-AMI showed the strongest correlation with the LVESV 3 months post-AMI ($r=0.76$, $p=0.001$), compared to EF ($r=-0.60$, $p=0.001$), global longitudinal strain ($r=0.56$, $p=0.001$), and LV apical rotation ($r=-0.53$, $p=0.001$). Furthermore, apical circumferential strain demonstrated the highest diagnostic accuracy: area under the receiver operating characteristic (ROC) curve 0.98, with sensitivity 100% and specificity 96% for prediction of LV remodeling, using a cutoff value $<-11.0\%$.

Conclusion: In patients with anterior AMI, LV apical circumferential strain in the early post-MI period constitutes a significant prognostic factor for LV remodeling at 3 months. Assessment of this parameter may identify patients at high risk for heart failure development.

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Left ventricular (LV) remodeling following acute myocardial infarction (AMI) is associated with higher rates of cardiovascular events.¹ It is characterized by progressive LV dilation, rearrangement of wall structure, myocyte hypertrophy, and increased muscle mass without an increase in wall thickness.¹

This initial myocardial dysfunction is further exacerbated by the persistence of humoral and mechanical factors.² Despite the introduction of primary percutaneous coronary intervention into daily practice for the management of AMI, the occurrence of LV remodeling in these patients remains high (about 30%), a percentage

almost similar to that seen in patients treated with thrombolysis (34%).³ Large infarct size and residual stenosis of the culprit lesion have been recognized as predictive factors for LV remodeling.³

LV function assessed by measurement of ejection fraction (EF) using conventional echocardiography is the initial evaluation for every patient who has suffered an AMI; it has significant prognostic value, but limited capability for risk stratification.⁴ The early identification of patients who are prone to develop remodeling post myocardial infarction has been the center of intense research in recent years, spearheaded by the introduction of new techniques in the field of cardiac imaging.^{5,6}

The purpose of the present study was to apply speckle-tracking echocardiography in patients with anterior ST-elevation AMI treated with primary transluminal coronary angioplasty (PTCA) in order to identify 1) global (LV longitudinal strain, LV torsion) and 2) regional (apical circumferential strain and rotation) echocardiographic parameters predicting LV remodeling.

Methods

Patient population

The study population consisted of 43 patients admitted for a first ST-segment elevation AMI. The diagnosis of AMI was based on a documented transient increase in biochemical markers of myocardial necrosis (creatinine kinase-MB and/or troponin I) and the presence of typical symptoms and/or electrocardiographic signs of AMI.⁷ All patients underwent PTCA and their TIMI frame count was assessed.⁸ Two-dimensional echocardiography and speckle-tracking analysis were performed four days and three months post AMI.

Echocardiography

Study participants were imaged in the left lateral decubitus position with a commercially available system (GE Vivid 7 Dimension system, Horten, Norway) with a 3.5 MHz (M4S) transducer and films were digitally stored in cine-loop format; analyses were subsequently performed offline with dedicated software EchoPAC (version 7.0 General Electric Medical Systems). Parasternal long-axis views were used to measure LV internal dimensions at end-diastole and end-systole, according to the recommendations of the

American Society of Echocardiography.⁹ LV end-systolic (ESV) and end-diastolic (EDV) volumes were obtained using the modified biplane Simpson's rule from the apical four- and two-chamber views, and the EF was calculated. Mitral early (E) and late (A) diastolic flow velocities were measured and the E/A ratio was calculated. The deceleration time of the mitral E wave was also measured.

Speckle-tracking analysis

Longitudinal strain

Gray-scale two-dimensional apical images of the LV (4-, 2-, and 3-chamber views) were obtained and longitudinal strain (LS)⁷ analysis of the LV was performed by speckle-tracking imaging, according to the recommendations of the European and American Societies of Echocardiography.¹⁰ Five consecutive beats in each view were stored digitally for off-line analysis. The frame rate was set between 50-100 frames/s,^{11,12} sector width was set as narrow as possible, and gain settings were optimized. For each view, three consecutive beats were analyzed and mean values were calculated for all parameters derived. After the cardiac cycle has been selected, the software prompts the operator to apply a region of interest in a "click-to-point approach" to delineate the endocardium. Subsequently the software automatically defines an epicardial and mid-myocardial line (region of interest, ROI) and processes all frames of the selected cardiac cycle. The software automatically validates the segmental tracking throughout the cardiac cycle and allows further adjustment of the ROI by the operator in order to improve tracking quality. Mean global longitudinal strain was calculated by averaging the global LS obtained automatically from each apical view.

Apical circumferential strain and torsional mechanics

Two LV short-axis planes were obtained at basal (at the level of the mitral valve) and apical (distally to the papillary muscles) levels. For the speckle-tracking analysis, in each image, the endocardial border was traced and the ROI was adjusted to fit the myocardium. Each short-axis image was automatically divided into 6 standard segments (septal, anteroseptal, anterior, lateral, posterior, inferior) and the LV rotation from the apical and basal short-axis images was calculated as the average angular displacement of the 6 standard segments by referring to the ventricu-

lar centroid, frame by frame. Counter-clockwise rotation was marked as a positive value and clockwise rotation as a negative value when viewed from the apex. The LV twist curve was generated by calculating the difference between apical and basal rotations at each corresponding time point. LV torsion was then calculated as the ratio between LV twist (in degrees) and LV diastolic longitudinal length (in cm) between the LV apex and the mitral plane.

Circumferential strain (CS) of the LV apex was calculated using the same apical short-axis cycle that was used for the calculation of the apical rotation. Apical CS was defined as the average CS of all 6 segments (generated as previously described) in a particular short-axis view. The role of conventional and speckle-tracking echocardiographic parameters in predicting LV remodeling (defined as a $\geq 15\%$ increase in LVESV at three months follow up) was assessed.¹³

Ten patients were randomly selected to assess the reproducibility of apical CS, and Bland–Altman analysis was performed to evaluate intraobserver and interobserver agreement. The mean difference $\pm 2SD$ for apical CS was $0.4 \pm 2.2\%$ for intraobserver and $2.5 \pm 3.6\%$ for interobserver agreement.

Statistics

Values are reported as mean \pm SD. The paired t-test was used for intra-group comparisons of the echocardiography measurements at 4 days and 3 months post-AMI. Independent-samples t-tests were used to compare baseline (4 days post-AMI) parameters of the patients with and without LV remodeling. Spearman's correlation coefficient was used to assess correlations of the measured parameters. Univariate logistic regression analysis was performed to evaluate the relation between the occurrence of LV remodeling at 3-month follow up and the following baseline (4 days post-AMI) variables: age, TIMI frame count after PTCA, LVEDV, LVESV, LVEF, LV global LS, peak LV torsion, peak apical rotation, apical CS and creatine phosphokinase (CPKmax). Univariate and multivariate linear regression models were used to identify parameters that had a significant correlation with LV remodeling at 3 months. The optimal cutoff value for the parameter with the strongest association with LV remodeling was determined by a receiver operator characteristic (ROC) curve. A p-value < 0.05 was considered statistically significant. The statistical software package SPSS for Windows, version 21 was used for the analysis (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

The baseline characteristics of the patients included in the analysis are depicted in Tables 1 and 2. The left anterior descending was the culprit artery in 100% of the patients. Both groups of patients had similar rates of concomitant stenoses $\geq 70\%$ in the left circumflex and right coronary arteries. One patient was excluded from further analysis because of poor quality images. At hospital discharge, patients received standard medical therapy, including beta-blockers, antiplatelets, statins and angiotensin-converting enzyme inhibitors (ACE-I) at the maximum tolerated doses.

LV remodeling

During the 3-month follow-up period, 13 patients developed LV remodeling. Patients who developed LV remodeling during follow up, at 4 days post-AMI had significantly higher serum CPKmax, indicating a larger infarct size, higher levels of serum leukocytes and reduced values of apical CS, LV global LS, LVEF, LVESVi, apical rotation and LV torsion or twist, in comparison to patients with no remodeling (Table 2). Table 2 shows various characteristics of the patients with and without LV remodeling 4 days and 3 months post AMI. By univariate analysis (Table 3), apical CS, global LV LS, LVEF, and CPKmax 4 days post MI were significantly associated with LV remodeling.

Spearman's correlation coefficient (univariate linear regression) for apical CS ($r=0.76$, $p=0.001$, Figure 1), EF ($r=-0.60$, $p=0.001$), global LS ($r=0.56$, $p=0.001$), and LV apical rotation ($r=-0.53$, $p=0.001$), all measured at 4 days post-MI, revealed a good correlation with the LVESV at 3 months. Furthermore, apical CS at 4 days post-AMI had a significant correlation with CPKmax (as an index of infarct size), ($r=0.516$, $p=0.001$). The change in LVESV between day 4 and 3 months post-AMI was significantly associated with the apical circumferential ($r=0.577$, $p=0.001$, Figure 2) and global longitudinal strain ($r=0.319$, $p=0.039$), measured at 4 days post-AMI.

When apical CS, global LS, CPKmax, and torsion at 4 days post-MI were entered into a multivariate linear regression model, apical CS was the parameter with the best correlation with LV remodeling at 3 months. By ROC curve analysis, an apical CS cutoff value of -11% , at 4 days post-MI, had a sensitivity of 100% and a specificity of 96%, for predicting LV remodeling at 3 months (Figure 3).

Table 1. Baseline characteristics of AMI patients without versus with LV remodeling.

| Characteristics | LV remodeling | |
|--|---------------|--------------|
| | No n=29 | Yes n=13 |
| Age (years) | 56 ± 13 | 57 ± 14 |
| Male/female | 23/6 | 9/2 |
| Arterial hypertension (%) | 39 | 36 |
| Diabetes mellitus (%) | 25 | 9 |
| Family history of CAD (%) | 21 | 18 |
| Hypercholesterolemia (%) | 40 | 27 |
| TIMI frame count | 39 ± 14 | 46 ± 28 |
| CPK max (IU/L) | 1742 ± 1350 | 3491 ± 1700* |
| WBC (cells/L) | 11.5 ± 3.0 | 16.0 ± 3.0* |
| Scrum creatinine (mg/dL) | 0.9 ± 0.4 | 1.0 ± 0.2 |
| Time from symptom onset to balloon angioplasty (min) | 231 ± 133 | 325 ± 208 |
| Coronary angiogram: | | |
| Proximal LAD (%) | 46 | 54 |
| Mid LAD (%) | 50 | 46 |
| Distal LAD (%) | 4 | 0 |
| Left circumflex artery (%) | 15 | 15 |
| Right coronary artery (%) | 20 | 20 |
| Medical therapy at discharge: | | |
| Antiplatelets (%) | 100 | 100 |
| ACEI or ARBs (%) | 86 | 30 |
| Beta-blockers (%) | 97 | 100 |
| Statins (%) | 100 | 100 |
| TIMI frame count | 39 ± 14 | 46 ± 28 |

*p<0.05. AMI – anterior myocardial infarction; LV – left ventricle; CAD – coronary artery disease; CPK – creatine phosphokinase; WBC – white blood cells; ACEI – angiotensin converting enzyme inhibitors; ARBs – angiotensin II receptor blockers; LAD – left anterior descending artery.

Table 2. Echocardiography parameters in patients with and without LV remodeling 4 days and 3 months post myocardial infarction.

| Echocardiographic parameter | Remodeling (n=13) | | | No remodeling (n=29) | | |
|-----------------------------------|-------------------|------------|-------|----------------------|-------------|-------|
| | 4 days | 3 months | p | 4 days | 3 months | p |
| Apical circumferential strain (%) | -7.3 ± 2.2 | -7.8 ± 2.8 | 0.372 | -18.9 ± 5.2* | -19.9 ± 5.3 | 0.198 |
| Global longitudinal strain (%) | -9.7 ± 1.9 | -9.7 ± 1.6 | 0.991 | -12.9 ± 2.9* | -16.0 ± 3.4 | 0.001 |
| LVEF (%) | 42 ± 7 | 35 ± 7 | 0.011 | 48.9 ± 6.3* | 52.8 ± 7.5 | 0.005 |
| LVEDVi (mL/m ²) | 62 ± 15 | 85 ± 14 | 0.001 | 57 ± 13 | 56 ± 11 | 0.823 |
| LVESVi (mL/m ²) | 36 ± 10 | 55 ± 12 | 0.001 | 29 ± 9* | 27 ± 7 | 0.002 |
| Mitral E/A ratio | 1.4 ± 0.9 | 1.52 ± 1.4 | 0.326 | 1.4 ± 1.4 | 1.4 ± 1.6 | 0.871 |
| Deceleration time (ms) | 205 ± 97 | 160 ± 55 | 0.326 | 195 ± 71 | 193 ± 46 | 0.854 |
| LVEDD (mm) | 49 ± 6 | 56 ± 4 | 0.002 | 49 ± 5 | 51 ± 5 | 0.039 |
| LVESD (mm) | 31 ± 7 | 37 ± 7 | 0.011 | 30 ± 7 | 30 ± 6 | 0.567 |
| LV twist (°) | 13.7 ± 5.7 | 10.9 ± 2.7 | 0.090 | 17.8 ± 5.3* | 18.1 ± 6.3 | 0.799 |
| LV torsion (°/cm) | 1.5 ± 0.5 | 1.1 ± 0.3 | 0.066 | 2.3 ± 0.8* | 2.2 ± 0.8 | 0.583 |
| Basal rotation (°) | -7.2 ± 3.4 | -6.1 ± 4.1 | 0.419 | -6.8 ± 4.4 | 7.0 ± 3.3 | 0.818 |
| Apical rotation (°) | 6.8 ± 4.8 | 4.8 ± 4.2 | 0.329 | 11.1 ± 4.0* | 10.9 ± 8.4 | 0.917 |

*p<0.05 for comparison with the corresponding 4 days post-myocardial infarction in patients with remodeling.

LV – left ventricle; LVEDVi – left ventricular end-diastolic volume index; LVESVi – left ventricular end-systolic volume index; LVEDD – left ventricular end-diastolic dimension; LVESD – left ventricular end-systolic dimension.

Discussion

The main finding of the present study is that in patients with an anterior AMI treated with PTCA, im-

paired apical circumferential strain early after the event has significant prognostic value for a deterioration in cardiac function. In the current study we eval-

Table 3. Univariate predictors of left ventricular remodeling 4 days post-acute myocardial infarction.

| Characteristics | Univariate OR (95% CI) | p |
|--|------------------------------|-------|
| Age | 0.993 (0.954 – 1.062) | 0.809 |
| CPKmax | 0.999 (0.999 – 1.000) | 0.008 |
| TIMI frame count | 0.981 (0.945 – 1.020) | 0.336 |
| LVEDVi (mL/m ²) | 0.974 (0.929 – 1.022) | 0.291 |
| LVESVi (mL/m ²) | 0.921 (0.853 – 0.995) | 0.038 |
| LVEF (%) | 1.166 (1.031 – 1.318) | 0.014 |
| Peak LV global longitudinal strain (%) | 0.701 (0.522 – 0.940) | 0.017 |
| Peak LV torsion (°/cm) | 2.690 (0.992 – 7.296) | 0.052 |
| Peak apical rotation (°) | 1.175 (1.011 – 1.460) | 0.054 |
| Apical circumferential strain (%) | 0.394 (0.193 – 0.804) | 0.010 |

Abbreviations as in Tables 1 and 2.

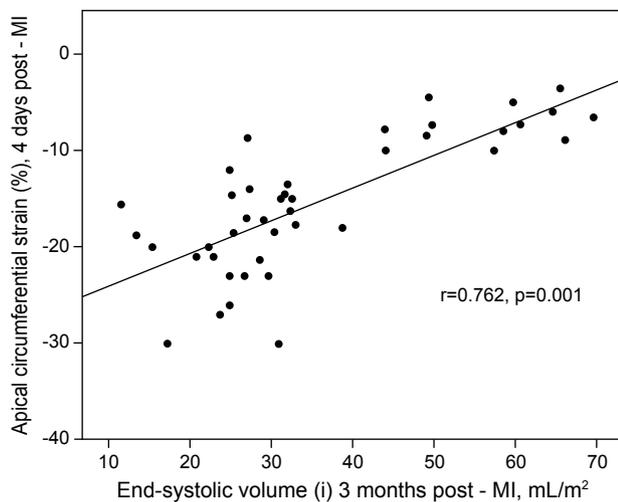


Figure 1. Correlation of apical circumferential strain 4 days post myocardial infarction with the left ventricular end-systolic volume index after 3 months.

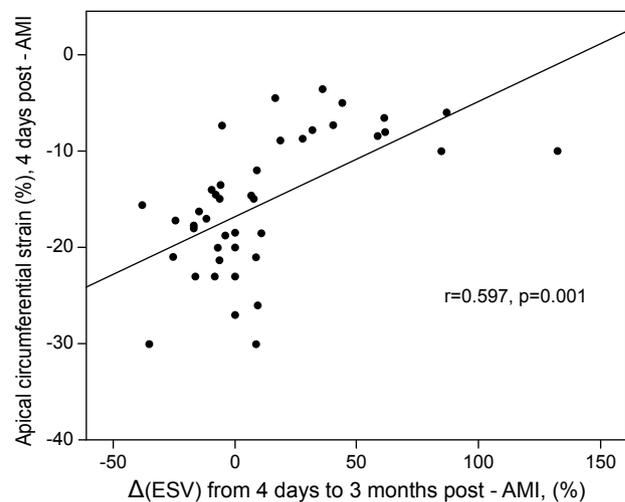


Figure 2. Correlation of apical circumferential strain values 4 days post acute myocardial infarction (AMI) with the difference (%) in the left ventricular end-systolic volume (ESV) from 4 days to 3 months post AMI.

uated LV function 4 days and 3 months post-AMI and found that 27.5% of the patients demonstrated LV remodeling. Compared to other echocardiographic parameters, apical CS was the strongest predictor of an increase in LVESV and LV remodeling at 3 months post-AMI.

Clinical and conventional echocardiographic parameters for prediction of LV remodeling

Remodeling occurs with different degrees of ischemic injury, though it is more pronounced in larger infarctions, making infarct size the key determinant. However, a critical infarct size above which dilation can-

not be compensated for has not been identified.^{14,15} In our study, the serum levels of the enzymatic marker CPK were significantly higher in patients who developed LV remodeling, a finding compatible with previous data.¹⁶ Furthermore, the presence of a higher leukocyte count on admission in patients with LV remodeling suggests the presence of a more extensive inflammatory process following AMI.¹⁷

Conventional echocardiographic parameters have long been used as markers for predicting LV remodeling.⁴ Previous studies have shown that LVEF constitutes a marker of LV remodeling. Similarly, in our study patients with LV remodeling at baseline had significantly lower LVEF and higher LVESV values,

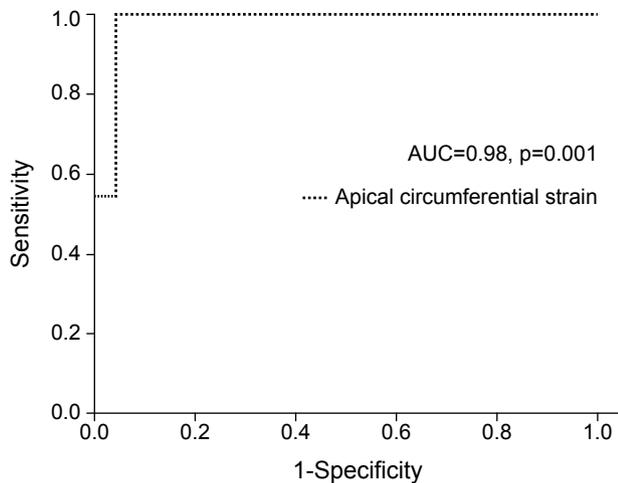


Figure 3. Receiver–operating–characteristic (ROC) curve shows that apical circumferential strain 4 days post acute myocardial infarction (AMI) is the best predictor (area under the curve, $AUC=0.98$, $p=0.001$) of left ventricular remodeling 3 months post-AMI. A cutoff point of -11% has a sensitivity of 100% and a specificity of 96% for identifying cases that will develop remodeling.

while no significant difference in the LVEDV was detected.^{13,18} Though these parameters have important prognostic value, they have limitations for risk stratification following AMI. One important reason for this limitation is that in the early post-infarction period the hypercontractility of the non-infarcted myocardial segments may result in overestimation of LVEF, despite the presence of significant regional LV systolic dysfunction.

Strain-derived LV mechanics in predicting LV remodeling

The adverse impact of remodeling on a patient's prognosis¹³ and the limitations of conventional echocardiography in identifying the post-AMI high risk patients, has triggered research into novel echocardiographic techniques, mainly speckle-tracking echocardiography, which provide a deeper insight into the physiology of cardiac mechanics.¹⁹⁻²¹ The method of speckle-tracking for calculation of strain is now routinely used. The main advantages of this technique over strain assessment based on Doppler tissue imaging are that measurements are angle independent, and that it can distinguish active from passive movement of wall segments. Strain-based parameters are sensitive indicators of regional and global cardiac function and have been extensively validated in ex-

perimental and human studies. Experimental studies in infarcted rats²² have shown that speckle-tracking derived CS correctly identifies segmental LV dysfunction that follows myocardial infarction. In the VALIANT study,²³ a reduced CS in the early post-infarction period was associated with a worse prognosis. Furthermore, Takeuchi et al²⁴ found that, in patients with anterior AMI, the presence of $EF < 45\%$ was correlated with depressed apical circumferential strain and rotation values. The impact of apical CS on LV function has been evaluated in a previous animal study, where the application of stem cells in the apex of the infarcted rat hearts improved the LV apical CS, the EF, and LV dyssynchrony.^{25,26} Additionally, in a cardiac resynchronization study, optimal LV lead position, defined by circumferential strain analysis, resulted in a greater improvement in LV function and more LV reverse remodeling than a non-optimal LV lead position.^{27,28} These data indicate that CS could be used not only for prognostic purposes, but also for the evaluation of potential therapeutic strategies in cardiomyopathies.

In our study, torsion and longitudinal deformation parameters of the LV at four days post-AMI were more impaired in patients who had remodeling later. Nucifora et al¹⁸ showed that the amount of impairment of LV torsion predicts LV remodeling at 6-month follow up. In that study, approximately 50% of the included patients had suffered an anterior myocardial infarction. Similarly, LS has been recognized as a global deformation parameter predicting LV remodeling, especially in patients with anterior myocardial infarction.²⁹⁻³¹ Furthermore, the type of infarction seems to have an impact on the cardiac deformation parameters. In a recent study, in the early post-infarction period, the infarct location, anterior or inferior, affected its impact on LV rotation.³²

In our study, apical CS was a stronger predictive marker of LV remodeling in comparison to LS. One potential pathophysiological explanation of this finding is suggested by a study where the presence of impaired mid-LV cavity CS had higher long-term prognostic significance compared to LS.²³ The investigators concluded that LV CS plays a more pivotal role in maintaining LV structure, and that worse circumferential CS might contribute to LV remodeling. In support of this hypothesis are the results of the study by Aikawa et al,³³ where in patients with an anterior infarction apical regional wall stress was an independent predictor of subsequent LV remodeling after AMI.

LV torsion and LS share the common characteristic that their values are derived both from myocardial segments affected by the ischemic insult and from segments that are not affected. As a result, in cases of moderate infarct size, increased contraction of the non-infarcted remote myocardium may potentially mask the extent of myocardial damage, leading to its underestimation. In our study, since apical CS was derived from the myocardial area supplied by the culprit left anterior descending coronary artery, its value was more representative of the extent of the ischemia-induced regional myocardial dysfunction.

Whether the impaired apical CS represents the extent of the infarcted myocardium, or in addition is also influenced by the contribution of stunned myocardium, warrants further research. In our study, CPK values were significantly more elevated in patients with LV remodeling, indicating larger infarct sizes.

Limitations

Only patients with an anterior myocardial infarction were included in the present study. Further studies are needed to identify the role of LV apical deformation in predicting LV remodeling in other infarct locations. In addition, although all efforts were made to obtain optimal acquisition of the two-dimensional images, image quality is a parameter that affects the accuracy of the speckle-derived strain. Furthermore, the contribution of infarct size and stunned myocardium to each echocardiographic deformation parameter needs further research, preferably involving more than one imaging modality. Finally, only 30% of the patients who developed remodeling could tolerate ACE-I or angiotensin II receptor blockers during their index hospitalization. Approximately 50% of them, four days post myocardial infarction, had an ejection fraction <40%. However, opinions still differ as to whether ACE-I should be given to all post-MI patients or specifically to high-risk patients only (i.e. EF<40%).³⁴ All patients who developed remodeling were on beta-blocker therapy.

Conclusions

During the early post-myocardial infarction period, LV apical CS constitutes a deformational parameter that can identify patients who are at risk of developing LV remodeling.

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