Prognostic value of left atrial strain quantification from 2D ultrasound imaging in post-ischemic heart failure patients: evidence from the REMODEL-HF study

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ABSTRACT

Background. Left atrial (LA) function can be effectively assessed by measuring longitudinal LA strain (LAS) via two-dimensional speckle tracking echocardiography (2DSTE). Here, we test 2DSTE-based LAS as marker of different left ventricle (LV) remodeling patterns and as prognostic index in ischemic heart failure (HF) candidates to surgical ventricular reconstruction.

Methods. We retrospectively considered ischemic HF patients with anterior (group A, n=130) or posterior (group P, n=48) LV remodeling. Based on 2D ultrasound, LV and LA morpho-functional parameters were quantified including reservoir (LAS Res), conduit (LAS Cond) and booster (LAS Boost) LAS. We tested their capability to discriminate between groups A and P, and their group-specific prognostic significance for the composite end-point of death or HF re-hospitalization at follow-up (mean follow-up time 48 months, range 3-101 months).

Results. Group A and group P displayed similar end-diastolic (p=0.89) and end-systolic (p=0.33) LV volume index, and LA volume index LAVi (p=0.44) corrected for the degree of mitral regurgitation. As compared to group P, group A revealed a significant reduction in LAS Boost (9.2±0.4% vs. 11.1±0.7%, p=0.04) and a non-significant reduction in LAS Res (16.9±0.7% vs. 19.3±1.1%, p=0.06).

Kaplan-Meier curves showed that the median LAS Res and LAS Boost values effectively stratified patients based on their prognosis in the overall study population (Log-rank p=0.002 and Log-rank p=0.0001) and in group A, where the association was stronger for LAS Boost (Log-rank p<0.001) than for LAS Res (Log-rank p=0.013).

Conclusions. 2DSTE-based LAS assessment is affordable, repeatable and non-invasive, and could add clinically-relevant mechanistic insight and prognostic value in the stratification of ischemic HF patients.

1. Introduction

Left atrial (LA) function is commonly described during three consecutive stages of the heart cycle, whereby the left atrium acts as elastic reservoir storing pulmonary venous return during ventricular systole, then as passive conduit for blood into the left ventricle (LV), and finally as active pump at late LV diastole [1] [2]. Hampered LA function has been identified as a relevant factor in the prognosis of heart failure (HF) patients [3]. Longitudinal LA strain (LAS), as measured by two-dimensional speckle tracking echocardiography (2DSTE), has recently emerged as an effective and highly reproducible descriptor of LA function [4]. Nonetheless, a recent survey from the EACVI Scientific Initiatives Committee highlighted that this technique is still poorly adopted in daily clinical practice, with less than 30% of the involved centers (96 European echocardiography laboratories) employing LA strain imaging [5].

LA and LV function are strictly related, i.e., the former is naturally linked to LV diastolic filling. Accordingly, one may argue that, at least in...
specific clinical scenarios, LV remodeling may be the driver of LA functional impairment. LA-LV interplay directly involves the mitral valve (MV) apparatus, and may thus be influenced by MV dysfunction, if any [6]. One of the most common MV dysfunctions is severe mitral regurgitation (MR), which is often associated with LA dysfunction [7] [8]. In ischemic HF, severe functional MR is often associated to progressive LV dilatation and has been already identified as an independent predictor of early and long-term mortality [9]. Functional MR is more frequently associated with posterior infarction, due to the involvement of the posterolateral papillary muscle [10]. However, in a previous study on a large cohort of patients undergoing surgical ventricular reconstruction (SVR), severe MR maintained its prognostic role only in patients affected by anterior infarction. That evidence suggested that severe MR in anterior and posterior LV remodeling may reflect dissimilar diseases, driven by a common ischemic etiology but displaying different mechanisms of disease progression depending on the location of the necrotic scar tissue [11]. Accordingly, it may be speculated that different LV remodeling patterns could also impact differently on LA function.

LA volume index (LAVi), routinely employed in clinical practice to assess LA size, has already been recognized as a valid indicator of poor SVR outcome in ischemic HF patients, though not reporting significant differences between anterior and posterior infarct [12]. However, in that study, only 32% of the enrolled patients had moderate to severe MR. Hence, the combined impact of severe MR and LA dysfunction on ischemic HF progression remains to be elucidated. Also, no previous study tested LA function potential in discriminating between different patterns of LV dysfunction and remodeling.

In the present study, we exploited 2DSTE to investigate the impact of different LV remodeling patterns on LA function in ischemic HF patients while ruling out the effect of MR severity. In addition, we analyzed a cohort of patients with severe primary MR and dilated LV, as a term of comparison.

Specifically, we tested two working hypotheses: i) different LV remodeling patterns, though displaying similar MR severity and LAVi, impact differently on LA function; ii) LAS measured by 2DSTE can add relevant information to the evaluation of ischemic HF patients during routine clinical practice.

2. MATERIAL AND METHODS

2.1. Study design

We retrospectively analyzed 208 patients eligible for surgery and enrolled from 2012 to 2020 in the REMODEL-HF Study, which was approved by the Local Ethics Committee (Protocol No 179/int/2019) and conformed to the principles of the Helsinki Declaration. The authors have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [13]. All patients, in sinus rhythm, underwent clinical and echocardiographic evaluation before surgery. Out of the 208 patients, 178 were ischemic HF candidates to SVR with no history of atrial fibrillation, namely (Figure S1):

- 130 patients with anterior LV remodelling (group A) and MR grade ≤2 (subgroup AM, n = 92) or MR grade >2 (subgroup AS, n = 38);
- 48 patients with posterior LV remodelling (group P) and MR grade ≤2 (subgroup PM, n = 15) or MR grade >2 (subgroup PS, n = 33).

In addition, a cohort of age-matched (57.03±12.36 years) patients with degenerative MV prolapse and severe MR (grade >2) (group DS, n = 30) was considered for the sake of comparison, in terms of LA strains, with subgroups AS and PS. This group was not considered in the survival analysis.

2D echocardiography

Two dimension (2D) transthoracic echocardiography was performed either with a Philips Epiq7 ultrasound system equipped with a X5-1 transducer (Philips Healthcare, Eindhoven, The Netherlands) or with a GE Vivid 7 ultrasound system (GE Healthcare, Waukesha, WI). The framerate of the acquired data ranged from 30 to 50 Hz (median frame rate 37 Hz).

LV end-systolic volume index (ESVi), end-diastolic volume index (EDVI) and LV ejection fraction (EF) were calculated with the Simpson’s biplane method. LAVi was measured from the apical 4-chamber view. The following indexes of diastolic function were assessed: peak blood flow velocity in early diastole (peak E wave) and in late diastole (peak A wave), and their ratio E/A; mean early diastolic mitral annular velocity (e’) from tissue doppler imaging (TDI) and the ratio E/e’.

Pulmonary arterial systolic pressure (PAPs) was computed combining tricuspid regurgitation (TR) jet velocity, derived using the simplified Bernoulli equation, with an estimate of the right atrial pressure by the diameter and collapsibility of the inferior vena cava [14]. MR was assessed using a 4-degree scale, based on the qualitative and semi-quantitative analysis of color and continuous wave Doppler imaging, focused on the trans-mitral regurgitant jet and on the presence of reversed flow in the pulmonary vein, respectively [15]. To feed 2DSTE analysis, 2D grayscale images of the LA chamber were acquired in the standard apical four- and two-chamber views using ECG-gated acquisition over 2 to 4 cardiac cycles, during a breath-hold.

The surgical procedure

All patients (group A and group B) underwent SVR under total cardiac arrest with antegrade crystalloid cardioplegia; details of the technique have been previously reported [16]. Complete coronary grafting was firstly performed when indicated, namely in 135 patients (76%); in the remaining patients, complete revascularization was achieved by previous successful percutaneous coronary intervention (PCI). Subsequently, the LV was opened to reduce and reshape the distorted LV cavity through the exclusion of the scar tissue.

2DSTE analysis

Off-line analysis was performed by an expert operator on each dataset: 81 patients (46%) were analyzed using the LA strain analysis tool available in TomTec (2D Cardiac Performance Analysis; TomTec Imaging Systems GmbH, Unterschleissheim, Germany); 97 patients (54%) were analyzed using the 2D-STE tool for LV strain analysis available in GE EchoPAC PC v204 (GE Healthcare, Waukesha, WI). In both cases, the LA endocardial border was manually traced at end-diastole, i.e., the frame following MV closure. Pulmonary veins and LA appendage were extrapolated across. The software automatically tracked LA endocardial motion over the cardiac cycle exploiting 2DSTE.

LA global function was quantified in terms of reservoir (LASRes), conduit (LASCond) and booster (LASBoost) longitudinal strain in the apical 4-chamber view (Figure S2), consistently with the latest recommendations from the EACVI guidelines and setting the zero strain reference at LV end-diastole [17]. LASRes was measured at the onset of MV opening, i.e., the cardiac frame with the maximum LA volume. LASBoost was measured at late diastole, i.e., at the onset of atrial contraction, detected either considering the p-wave on the ECG trace or, in case of unclear p-wave feature on the ECG trace, directly measuring the strain value at the end of the plateau on the LA strain curve. LASCond was computed as the difference between LASRes and LASBoost.

Intra- and Inter-Operator Variability Analysis

We assessed intra- and inter-operator variability of LASRes and LASBoost (Table S1). Inter-operator variability was assessed by comparing measurements by two independent and double-blinded operators on 20 randomly selected datasets. To assess intra-operator variability, operator 1 repeated the measurements twice on the 20 datasets; the second analysis, blinded to the first one, was performed at least two weeks later.

Inter-Vendor Variability Analysis

As LAS was assessed with two different software packages, inter-vendor variability of LAS analysis was carried out on 22 datasets: 18 datasets of group A (including 7 datasets of group AS) and 4 datasets of
group P (including 3 datasets from group PS). Upon verifying the Gaussian distribution of data, the LAS_{Boost} and LAS_{Res} values yielded by the two software packages were compared by paired t-test, Bland-Altman analysis, and Pearson correlation.

2.2. Statistical Analysis

Statistical analyses were performed in GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS 26.0 (Statistical Package for the Social Sciences, Chicago, Illinois). Data for categorical variables were presented as proportions and continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR). Normality of data distributions was assessed through Shapiro–Wilk test. A P-value of <0.05 (α) was considered statistically significant.

Data from intra-operator and inter-operator variability analyses were compared through Bland–Altman analysis (bias and 95% limits of agreement), Pearson correlation, intraclass correlation coefficient (ICC) and coefficient of variation (CV).

Differences between groups A and P were assessed by means of analysis of variance with adjustment for MR severity and reported as least-square means (± standard error).

The prognostic significance of LAVi and LAS parameters (with the median value used as cut-off) was tested for the composite end-point of death or HF re-hospitalization at post-surgery follow-up (mean follow-up time = 40 months, range 3–101 months) in the overall ischemic HF population and in groups A and P separately. Survival analyses were displayed through Kaplan-Meier curves and the Log-Rank test. LAS and LAVi displayed through Kaplan-Meier curves and the Log-Rank test. A P-value of <0.005 (α) was considered statistically significant.

The analysis focusing on AS and PS subgroups with severe MR was accomplished as follows: for each ultrasound-based index, univariate binary logistic regression was used to estimate the odd ratio (OR) of association to the different pattern LV remodeling, using the dichotomous AS/PS classifiers as response variables; ORs precision was determined through 95% confidence interval. Also, the Pearson correlation coefficient (r) was used to measure the strength of association between the variables extracted from subgroups AS and PS.

Finally, Kruskal-Wallis one-way analysis of variance with post hoc Dunn’s multiple comparisons were carried out to investigate differences among AS, PS and DS subgroups.

3. RESULTS

Baseline clinical characteristics of the enrolled patients are detailed in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=178)</th>
<th>Myocardial infarction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>144 (80.9)</td>
<td>102 (130)</td>
<td>0.17</td>
</tr>
<tr>
<td>Female</td>
<td>44 (29.1)</td>
<td>42 (48)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤69 years</td>
<td>64 ± 9</td>
<td>63 ± 10</td>
<td>0.20</td>
</tr>
<tr>
<td>&gt;69 years</td>
<td>104 (58.3)</td>
<td>77 (53.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hypertension</td>
<td>102 (57.3)</td>
<td>77 (53.2)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>108 (61.7)</td>
<td>80 (56.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes (or medication)</td>
<td>41 (23.4)</td>
<td>34 (26.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>NYHA class ≥3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>79 (45.4)</td>
<td>54 (42.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Class II</td>
<td>75 (42.2)</td>
<td>51 (41.2)</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>13 (7.4)</td>
<td>11 (9.1)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>135 (75.8)</td>
<td>95 (78.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>MV surgery</td>
<td>66 (37.1)</td>
<td>39 (30.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age expressed as mean ± SD; all the other variables expressed as number of patients (relative percentage with respect to total or group-specific numerosity).</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LA strains in anterior and posterior LV post-ischemic remodeling

Patients with anterior LV remodeling due to myocardial infarction (group A) reported markedly lower EF (p=0.003) than patients with posterior LV remodeling (group P), with mean EF values adjusted for MR grade equal to 30.2% and 33.9%, respectively (Table 2). Also, group A exhibited increased PAPs (43.8±1.2 vs 30.8±2.0 mmHg, p<0.001) and augmented diastolic function indexes of E/A (1.6±0.1 vs 0.9±1.5, p<0.001) and E/e’ (17.4±0.6 vs 13.9±1.0, p=0.004) when compared with group P. Differences between the two groups remained negligible in terms of EDV (p=0.89), ESV (p=0.33) and LAVi (p=0.44). LA function significantly differed between group A and P in terms of LAS_{Boost} (p=0.04), reporting lower values in group A (9.2 ± 0.4 %) than group P (11.1 ± 0.7 %). Also, in group A, LAS_{Res} remained lower, though not significantly (p=0.06), than group P (16.9 ± 0.7 % vs. 19.3 ± 1.1 %, respectively); no differences emerged when comparing LAS_{Cond} (p=0.47).

Survival analysis was performed for each LAS value in the overall post-ischemic HF population, and in groups A and P separately (Figure 1).

In the overall post-ischemic HF population, regardless of the LV-specific remodeling conditions (Figure S3), both LAS_{Res} and LAS_{Boost} showed a significant prognostic value (Log rank p=0.002 and Log rank p<0.0001, respectively) comparable to the one reported by LAVi (Log rank p=0.003). These results are confirmed by the Cox univariate analysis displaying p<0.005 for LAS_{Res}, LAS_{Boost} and LAVi (Table S5).

In group A, both LAS_{Res} and LAS_{Boost} proved significantly associated with prognosis: patients with LAS_{Res} and LAS_{Boost} values lower than the respective median value, i.e., 16.8% (Figure 1a) and 9.7% (Figure 1c), showed a much higher incidence of adverse events than those with LAS values higher than medians. Such association was stronger for LAS_{Boost} (Log rank p<0.001) than for LAS_{Res} (Log rank p=0.013), though both variables reported a more relevant prognostic value than LAVi (Figure 1e, Log rank p=0.03).

Conversely, in group P, association with higher mortality rates revealed not to be statistically significant, being Log rank p=0.32 for LAS_{Res} (Figure 1b), Log rank p=0.42 for LAS_{Boost} (Figure 1d), Log rank p=0.28 for LAVi (Figure 1f) and Cox univariate analysis p>0.29 (Table S5). LAS_{Cond} was not associated with the occurrence of adverse events neither in Group A (Log rank p=0.13) nor in Group P (Log rank p=0.41).

Focus on severe MR

When focusing on AS and PS subgroups with severe MR, at univariate logistic regression (Figure 2a), anterior LV remodeling was associated with a decrease in both LAS_{Res} (OR [95% CI]=0.92 [0.85–1.00], p=0.045) and LAS_{Boost} (OR [95% CI]=0.85 [0.75–0.97], p=0.015), with a decrease of EF (OR [95% CI]=0.89 [0.82–0.97], p=0.005), and with an increasing in PAPs (OR [95% CI]=1.08 [1.04–1.13], p<0.001) and E/A (OR [95% CI]=2.27 [1.24–4.13], p=0.008) (Table S2). At

Table 2

Results of 2D echo-based comparison, in terms of LV and LA function, between anterior (group A) and posterior (group P) phenotypes of ischemic LV remodeling. Data are adjusted for the severity of mitral regurgitation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=130)</th>
<th>Group P (n=48)</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDVi [ml/m²]</td>
<td>122.3 ± 2.9</td>
<td>122.4 ± 5.1</td>
<td>0.89</td>
</tr>
<tr>
<td>ESVi [ml/m²]</td>
<td>86.7 ± 2.6</td>
<td>81.5 ± 4.5</td>
<td>0.33</td>
</tr>
<tr>
<td>EF [%]</td>
<td>30.2 ± 0.6</td>
<td>34.0 ± 1.0</td>
<td>0.003</td>
</tr>
<tr>
<td>PAPs [mmHg]</td>
<td>43.8 ± 1.2</td>
<td>35.8 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e’ [-]</td>
<td>17.4 ± 0.6</td>
<td>13.9 ± 1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>E/A [-]</td>
<td>1.6 ± 0.1</td>
<td>0.9 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAVi [ml/m²]</td>
<td>46.9 ± 1.2</td>
<td>48.9 ± 2.1</td>
<td>0.44</td>
</tr>
<tr>
<td>LAS_{Res} [%]</td>
<td>16.9 ± 0.7</td>
<td>19.3 ± 1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>LAS_{Boost} [%]</td>
<td>7.6 ± 0.4</td>
<td>8.2 ± 1.6</td>
<td>0.47</td>
</tr>
<tr>
<td>LAS_{Cond} [%]</td>
<td>9.2 ± 0.4</td>
<td>11.1 ± 0.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adjusted values reported as least-square means (± standard error).
Figure 1. Kaplan-Meier survival curves (Log-Rank p values) for death and HF combined endpoints, at 6-years follow up. Analysis have been carried out for anterior (group A, left panels) and posterior (group P, right panels) myocardial infarction groups, separately. A, B) LAS\textsubscript{Res}; C, D) LAS\textsubscript{Boost}; E, F) LAVi. Red curves: patients displaying LAS or LAVi values lower than the median value of the relative group; blue curves: patients displaying LAS or LAVi values higher than the median value of the relative group.
multivariate analysis, both EF and PAPs remained independently associated to the type of LV remodeling (i.e., OR [95% CI]=0.82 [0.71÷0.94], p=0.005 and 1.18 [1.07÷1.30], p=0.002 for EF and PAPs, respectively).

All the variables analyzed in subgroups AS and PS were correlated with each other. Interestingly, the correlation matrix (Figure 2b) revealed a significant (p<0.001) negative association for both LAS_{Boost} and LAS_{Res} with E/A and PAPs, respectively. Specifically, LAS_{Boost} reported a strong Pearson correlation with E/A (R=-0.71) and a moderate correlation with PAPs (R=-0.51). Lower values of moderate correlation were noticed for LAS_{Res} with respect to E/A (R=-0.61) and PAPs (R=-0.46) (further details in Table S3).

More in depth, these correlations proved to be dependent on the specific pattern of LV remodeling (Figure 2c-d): negative LAS_{Boost} and LAS_{Res} correlations with E/A and with PAPs were found in both the PS and AS subgroups, but in the PS subgroup correlations with E/A were mildly weaker (r=-0.57 vs. r=-0.72 for LAS_{Boost}; r=-0.47 vs. r=-0.60 for LAS_{Res}) and correlations with PAPs were notably weaker (r=-0.29 vs. r=-0.55 for LAS_{Boost}; r=-0.23 vs. r=-0.53 for LAS_{Res}).

Furthermore, AS and PS subgroups were compared with a cohort of patients with severe MR and dilated LV due to organic MV prolapse (group DS). Despite a comparable degree of MR severity, AS and PS patients showed a significantly reduced EF as compared to DS patients (p<0.001) in association with larger EDVi (p<0.001), larger ESVi (p<0.001), and comparable LAVi (p=0.08). Also, post-hoc analysis showed that, as compared to DS patients, significantly lower LAS_{Res} values characterized AS patients (p<0.001) and PS patients (p=0.004).

Interestingly, only AS patients (p=0.039) and not PS patients (p>0.999) showed reduced LAS_{Boost} values as compared to DS patients (Table S4, Figure S4).

**Intra- and inter-operator variability of LAS quantification**

Intra-observer analysis for both LAS_{Res} and LAS_{Boost} displayed excellent agreement in terms of Pearson correlation (Pearson r equal to 0.96 and 0.94, respectively) and ICC (above 0.97 for both LAS_{Res} and LAS_{Boost}). The Bland-Altman analysis showed clearly small differences introduced by the two different measurements. Inter-observer analysis results for both variables displayed slightly greater bias and wider 95% limits of agreement range but also very high coefficients of correlation.
We retrospectively analyzed a population of post-ischemic HF patients with either anterior (group A) or posterior (group P) infarct, with different levels of MR severity but with comparable severity of LV dysfunction as quantified by global indices. Group A patients and group P patients had statistically equivalent EF values; the respective EF values were both below 35% and differed by less than four percentage points on average even if this small difference was statistically meaningful.

Based on the tight functional relationship between the LV and the left atrium, we measured LAS in this population via 2DSTE to test if these could i) provide extra mechanistic insight into the different patterns of LV remodeling following anterior and posterior infarct, ii) be suitable to support prognosis in post-ischemic HF patients, and iii) have a superior prognostic value as compared to LAVi.

**Mechanistic insight into post-ischemic LV remodeling following anterior and posterior infarct**

The reduction in LAS observed in our post-ischemic patients may be interpreted as the consequence of the increased afterload experienced by the left atrium, which reflects the reduced LV diastolic compliance associated with myocardial necrosis [18]. Indeed, this interpretation is particularly supported by the analysis we performed specifically on the patients affected by severe MR to rule out the possible confounding effect of different degrees of MR. In this sub-population, LASres and LASBoost were negatively and significantly correlated with PAPs at univariate analysis (Figure 2b). Such correlation was stronger in patients with anterior infarct (AS group) than in patients with posterior infarct (PS group) (Figure 2c-d), consistently with larger scarred region typically characterizing the LV wall in case of anterior infarct [19], leading to more pronounced LV wall stiffening and LV diastolic compliance reduction.

The difference between anterior and posterior infarct in our study population was highlighted in particular by LASBoost, statistically significant differences were found when considering our whole population and correcting for the severity of MR (Table 2), despite the very similar volumetric remodeling of the LV chamber in the two classes of patients. Such differences were confirmed when focusing on the AS and PS groups and comparing these to patients affected by degenerative severe MR (DS group): in this case, statistically significant differences in LASBoost were found between AS and PS patients, between AS and DS patients, but not between PS and DS patients. The third result is consistent with the fact that in PS patients the necrotic myocardium likely affects a limited region of the LV wall, thus leading to comparable global diastolic LV compliance vs. DS patients, whose LV wall is free from necrosis.

Lastly, we may speculate that LA size (namely LAVi) is a mirror of MR severity, while LA function (namely LAS) reflects the severity of LV remodeling, in turn linked to the different localization of the infarct. Notably, in our study LAS analysis was capable of discriminating between different localizations of LV infarction even in presence of severe MR and severely dilated LA volume; in other words, LAS proved to be such a sharp marker of LV post-ischemic function that it was barely affected even by major confounding factors related to LA function.

**LA strain assessment to support prognosis in post-ischemic HF patients**

Carluccio and colleagues showed that LAS as assessed by 2DSTE can help the prognosis in a population of HF patients; 38% of those were post-ischemic patients [3]. More recently, Kim and colleagues showed in a wide population of post-ischemic patients that LAS assessed by 2DSTE or by magnetic resonance imaging yields incremental diagnostic value as compared to LA geometry for stratifying presence and severity of diastolic dysfunction, and improves the prediction of post-ischemic HF [20]. Consistently, we found that both LASBoost and LASRes have a prognostic value in our population: even simple median cut-offs allowed to discriminate between the patients who died or were rehospitalized because of HF at follow-up and those who did not. This result suggests 2DSTE-based LAS assessment as an attractive means to improve patient prognosis and stratification, as this procedure is fast, cheap, non-invasive, and, as confirmed by our intra- and inter-operator variability analysis (Table S1), sufficiently repeatable. However, this result, obtained when considering the entire study population, was confirmed when the analysis was restricted to the patients with anterior infarct only, but not when considering only those affected by posterior infarct (Figure 1). This evidence parallels the one by Garatti et al. [11], who reported the prognostic value of MR severity yields in post-ischemic patients affected by anterior infarct, but not in those affected by posterior-infarct. Based on those data and on ours, we speculate that LAS assessment should be more widely adopted to aid the stratification of post-ischemic HF patients, but only upon considering the underlying LV remodeling mechanism related to the original location of the infarcted region. This finding represents the novel aspect of the present work, which adds a caveat to the previous findings on the prognostic utility of LAS.

Remarkably, in our study population LAVi was not capable of discriminating between group A and group P patients, also revealing to be weaker than LASres and LASBoost in predicting the occurrence of adverse events at follow-up.

**Limitations**

The present study has seven main limitations. First, it is based on a retrospective analysis; thus, it was not possible to collect the data on every potentially relevant variable for each considered patient. For instance, we could not consider PAPs values for the DS group patients, which could have enriched the comparison of the two post-ischemic scenarios, i.e., anterior and posterior infarct, against a scenario with an unscarred LV wall. Also, we had data from late gadolinium enhancement (LGE) sequences of cardiac magnetic resonance imaging only for a strict minority of the considered patients; therefore, we could not test more intensively the relationship between LAS impairment and site/extent of necrotic myocardium as assessed by LGE images.

Second, the extent of the follow-up timeframe is very variable (range 3-101 months) in the considered population of post-ischemic patients. The presence of patients with a rather short follow-up period may have led us to underestimating the incidence of adverse endpoints, potentially impacting on our conclusions regarding the prognostic value of LASBoost and LASres.

Third, the numerosity of the A group (n=130) and of the P group (n=48) was very different, which may have impacted on our analysis of inter-group differences. However, this uneven distribution reflects the actual incidence of the two infarct phenotypes in the real post-ischemic population [21]. Also, this limitation disappeared when we focused only on post-ischemic patients with severe MR, as the AS and PS groups have very similar sample sizes.

Fourth, LAVi and LAS were measured based on the apical 4-chamber view only, with no bi-plane assessment. Indeed, for a relevant fraction (n=35, i.e. 20%) of the examined population, LAVi was not measurable in the 2-chamber view being it either absent or of insufficient quality as the LA was only partially captured in the field of view, due to the severe adverse remodeling. Even a larger number of patients displayed 2-
chamber views where only a minor portion of the atrial wall was not visible, thus guaranteeing a good approximation of LAVi computation, but yet hindering LAS measurement. The latter, indeed, fails when even a small portion of the endocardial contour cannot be tracked by speckle tracking. The difference between LAVi as computed through the single 4-chamber plane approach and through the biplane method was assessed considering the patients with an adequate 2-chamber view and has been reported in the Supplementary Material (Figure S6).

Fifth, echocardiographic acquisitions were characterized by a relatively low frame rate, which almost never exceeded 60 Hz. This feature may impact the reliability of speckle tracking-based measurements of LA strains. However, previous findings on synthetic 2D ultrasound images and on 2D ultrasound acquisitions on real patients by Rösner and colleagues showed that, as long as the frames per cardiac cycle fell in the range 26-85 Hz, no statistically meaningful differences in strain values are detected [22].

Sixth, MR severity was graded based on qualitative and semi-quantitative measurements.

Lastly, the number of events recorded for the combined endpoint of death and HF hospitalization (n range 26-85 Hz, no statistically meaningful differences in strain values) but yet hindering LAS measurement. The latter, indeed, fails when even a minor portion of the atrial wall was not

**References**


