

Left atrial strain in cardiovascular diseases: an overview of clinical applications

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Background

Thanks to the increasing evidence on the importance of left atrial (LA) function over LA dimensions to evaluate cardiovascular disease, and to the publication of multicenter data for reference values and to the recent European association of cardiovascular imaging (EACVI)/American society of echocardiography (ASE) consensus document for its standardization (1–3), LA strain by speckle tracking echocardiography (STE) is gaining visibility for the application in daily clinical practice. This parameter allows to analyze LA myocardial deformation and to recognize also concealed myocardial damage (4). Therefore, being non-invasive, quick and easy to perform, LA strain could offer precious information to basic echocardiography, with high diagnostic and prognostic accuracy, often comparable to other advanced imaging modalities (5). The aim of the present review is to discuss the clinical application of LA strain by STE based on the available evidence.

LA strain measurement

STE is a non-Doppler semi-automatic technique which was born to study left ventricular (LV) chamber but has then been successfully applied also to other chambers, with recent development of a dedicated software also for LA strain measures. *Table 1* resumes the methodological characteristics of LA strain performance by STE (6). There are two modalities for the use of reference ECG-trace starting point for LA strain: using Q-wave as starting point, LA deformation analysis begins with LA relaxation, therefore a positive curve will be produced; using P-wave as starting point, the cycle will include LA

TABLE 1. Methodological requirements and details of speckle tracking analysis for the measurement of left atrial strain. ECG; electrocardiogram; Fps, frame-per-second; LA, left atrium; ROI, region of interest

Image acquisition
LA apical four- and two-chamber view (optional) images obtained using conventional two-dimensional gray-scale echocardiography
use dedicated LA view, avoiding LA foreshortening
acquire during a brief breath hold
stable ECG recording is required
three-consecutive heart cycles registered for each clip
frame rate required: 60-80fps
store and analyze offline in a dedicated workstation
Software semi-automatic analysis
Manually trace the LA endocardium in both four- and two-chamber (if available) views by a point-and-click approach
The system automatically identifies an endocardial ROI of 6 segments, that can be manually adjusted in width and shape
The software flags correctly and non-correctly identified segments, allowing modifications or re-calculation of ROI
After final acceptance of the ROI traced, the software generates the longitudinal strain curves of all segments together with average curve of all segments
Results and calculation of LA strain
Each curve is representative of the movement of “speckles”, or pixels of LA wall, which distancing from each other will produce a positive curve, while their getting closer (i.e. contraction) would produce a negative curve
The average curve describes the phases of global LA deformation all over the cardiac cycle
P-wave or QRS could be used as reference starting point (QRS- method is slightly superior in rapidity and feasibility (7))

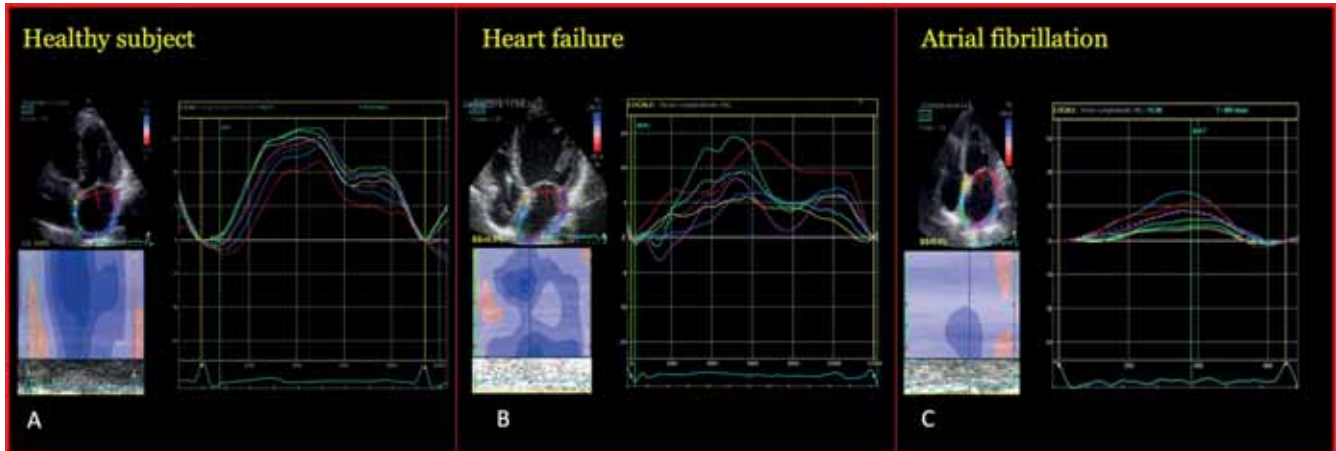


FIGURE 1. Difference between LA strain curve in a normal subject (PANEL A) with presence of preserved peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS), in a patient with heart failure (PANEL B), with reduced PALS and PACS, and a patient with atrial fibrillation, in which PALS is impaired and PACS is absent (PANEL C), due to the lack of atrial contraction

systole, thus, there will be an initial negative curve (= LA shortening) followed by a positive curve. A recent multicenter study by the young community of the EAC-VI involving senior and young operators has shown a slight superiority of QRS-method in terms of feasibility and time-consumption than P-wave method (7).

From the R-wave LA strain curve the following parameters could be assessed (Fig. 1):

- Peak atrial longitudinal strain (PALS), corresponding to LA early diastolic reservoir phase with maximum relaxation of LA wall (reference value: in the general population 39% [95% confidence interval – CI – 38–41%]) (2).
- Peak atrial conduit strain, corresponding to LA mid-diastolic emptying phase with LA passive shortening (reference value: 23% [95% CI: 21–25%]).
- Peak atrial contraction strain (PACS), corresponding to late-diastolic LA systole for the active LV filling (reference value: 17% [95% CI: 16–19%]).

PALS is currently the most utilized LA strain parameter, for its proven utility both in patients in sinus-rhythm and with atrial fibrillation (AF) in many clinical settings.

Importantly, the abovementioned reference values are referred to a healthy medium-age population. The effect of age and training on LA deformation should be considered in the evaluation of the specific subject (8–11).

Heart failure

Even if heart failure (HF) has traditionally been considered a LV disease, in the last decades more attention has been given to the involvement of LA in HF. In fact, the assessment of LA dimensions and function has shown to be essential in both HF with reduced and preserved ejection fraction (HFrEF and HFpEF) for diagnosis, prognosis, and to guide therapeutic strategies (12, 13).

Heart failure with reduced ejection fraction

In patients with chronic HF, the LA faces the gradual increase of LV filling pressure, initially dilating to increase its contribution to LV filling, up to a point in which a maladaptive remodeling overcomes with LA enlargement and fibrosis, leading to LA dysfunction. This often coincides with the onset of HF typical symptoms and arrhythmias (14) and represents the last step before the development of pulmonary hypertension (PH) and the transition to biventricular advanced HF, which entails considerably worse prognosis.

PALS has shown to be an accurate index of LV filling pressures, and to have a strong association with elevated pulmonary capillary wedge pressures both in patients with HFrEF and HFpEF (15, 16).

In HFrEF, PALS has been correlated with highest burden of symptoms and reduction of functional capacity (14). Also, it has been found to be of particular utility for the prognostic assessment over LV parameters: Carluccio et al. have shown that $PALS \leq 15.5\%$ proved to be far superior to LA volume and $GLS \leq 7.9\%$ (absolute value) for the overall prediction of HF hospitalization and all-cause death (area under curve, AUC 0.75, 0.70 and 0.68 respectively, $p < 0.01$) (17). In a recent study, PALS offered a good risk stratification in a cohort of stable patients with chronic HFrEF and was an independent predictor of a composite outcome of HF hospitalization, cardiovascular (CV) mortality, non-fatal myocardial infarction or stroke (hazard ratio(HR)=0.95; 95% CI: 0.94–0.96; $P=0.02$); and lower PALS corresponded to an increased incidence of AF (18). Fig.1 shows a typical reduction of PALS and PACS in a patient with HFrEF.

Heart failure with preserved ejection fraction

HFpEF is often described as “diastolic HF” since, despite preserved LV systolic function, a subtle impairment of left chambers relaxation properties, often related to

the presence of comorbidities such as hypertension, AF, diabetes mellitus and obesity, leads to the increase of LV filling pressures and consequent LA dilatation and dysfunction. LA strain is the most used strain parameter in HFpEF, due to its great power for the study of LV diastolic dysfunction, LV filling pressures and AF onset in these patients (19). Also, it provided important prognostic information in HFpEF (20).

In fact, in a cohort of 363 patients hospitalized for dyspnea, LA reservoir showed the best accuracy for diagnosing HFpEF (AUC 0.719; $P < 0.0001$) outperforming other known diastolic indices and LV strain (21); moreover, *Freed et al.* showed that abnormal LA reservoir, conduit, and booster pump strain were associated with increased events (CV hospitalization and all-cause mortality), and worse PALS was associated with reduced cardiac output and decreased peak oxygen consumption (VO_2); moreover LA strain was a predictor of CV events independently from GLS and right ventricular (RV) strain and properly stratified the risk of 308 patients with a cut-off value of PALS $\leq 31.2\%$ ($p < 0.009$) (22).

Furthermore, *Morris et al.* have analyzed a cohort of 517 patients at risk for LV diastolic dysfunction with preserved EF, showing that LA strain provided incremental diagnostic accuracy for LV diastolic dysfunction (raising the rate of detection from 13.5% to 23.4% compared to the use of LA volume index (LAVI) alone; $p < 0.01$) with PALS $< 23\%$ being associated with worse NYHA class even in presence of normal LAVI (23).

As the classification of diastolic function is crucial for the evaluation of patients with HFpEF in order to reach a tailored therapeutic approach, in light of the previous evidence, PALS has been proposed as an additional index to include in the currently recommended algorithm for the detection of diastolic dysfunction (24) to better classify those patients falling in the “grey zone” of “undetermined” diastolic function (25).

Atrial fibrillation

AF is one of the most common CV diseases, with a great epidemiological, clinical and economic impact on healthcare services. Therefore, noninvasive tools to assess AF onset and possible relapse after different therapies would be useful for daily clinical practice. Being an early marker of altered atrial structure and function, LA strain has shown an important role for the diagnostic and prognostic study of AF patients (26). Notably, for LA strain calculation in patients with AF, images with 5 cardiac cycles should be registered and then analyzed, and that the final curve will be slightly different, since PACS would be absent due to the lack of LA contraction (*Fig. 1*).

Prediction of AF onset

AF is often caused by myocyte interstitial deposition of collagen fibers causing massive LA fibrosis, with con-

sequent alterations in normal electrical conduction. Moreover, the progressive increase of LA fibrosis favors the conversion to a permanent AF form. Therefore, the prevention of atrial fibrosis would be essential to prevent AF onset and progression, and the identification of an advanced stage of fibrosis can guide the choice of the best therapeutic strategy. Even though cardiac magnetic resonance (CMR) is the gold standard method to assess myocardial fibrosis, it is limited by high costs and low availability. *Kuppahally et al.* have demonstrated an inverse relationship between the grade of fibrosis measured by CMR late gadolinium enhancement and LA strain, particularly in patients with persistent AF compared to paroxysmal forms (27). This suggests a link between AF duration, interstitial atrial remodeling and LA mechanical dysfunction. *Petre et al.* identified PALS and PACS as predictors for AF occurrence, with a good accuracy AUC=0.88 for PALS and AUC=0.86 for PACS in a hypertensive cohort with/without history of AF (28).

Prediction of AF recurrence

The main therapeutic approach for patients with AF to restore sinus rhythm is electrical or pharmacological cardioversion. Although the initial success of electrical cardioversion has been reported as greater than 90%, approximately 50% of patients relapse into AF within 1 year (29). If cardioversion repeatedly fails, a transcatheter or surgical ablation therapy should be tried.

LA strain proved to be an important predictor of AF recurrence after cardioversion over a 6-month follow-up: PALS improvement resulted to be higher in patients who maintain sinus rhythm than those with relapse episodes (30). However, PALS predictive capacity of sinus-rhythm maintenance is even higher in subjects who undergo ablation.

In fact, the grade of atrial remodeling plays a fundamental role in AF ablation success. Baseline PALS resulted to be an independent predictor of LA reverse remodeling in patients undergoing ablation: this because if PALS is severely impaired, LA fibrosis could be at a more advanced stage and might be irreversible (31, 32). Moreover, LA strain at reservoir phase predicts maintenance of sinus rhythm after ablation in both paroxysmal and persistent AF forms: the lack of a significant increase of global PALS after the procedure suggest the possibility of new episodes of arrhythmia (33). Bearing that this intervention is not free of risks, accurate selection of patients is essential, and LA strain would be of great utility to identify patients with high risk of AF recurrence, as shown in a recent meta-analysis including 8 studies (34).

Prediction of thromboembolic risk

It is known that, in patients with AF, the loss of atrial contractility and blood stasis in LA facilitate thrombus development, mostly located in LA appendage (LAA).

LA strain has shown to be a promising tool in the risk assessment of thromboembolic risk (35), as shown in a large multicenter registry including 1361 patient with first episode of AF (36). Interestingly, a recent study by *Alhakak et al.* showed that the measurement of PALS in general population offered adjunctive information on the prediction of AF and stroke over a long follow up (16 years), particularly in patients <65 years (HR 1.46 per 5% decrease at multivariable analysis; 95% CI: 1.06–2.02; P=0.021) (37).

Decreased PALS was independently associated with LAA dysfunction <7 days of onset of acute ischemic stroke (38). In another study, LA strain reduced parallel with CHADS2 score and the association between CHADS2, LA strain and LA volume gave additional value for risk stratification (39). On the other hand, LA strain has in fact been proposed as a tool to identify patients with AF after cryptogenetic stroke (40). In fact, *Rasmussen et al.* showed that, in a cohort of patients with cryptogenetic stroke, unlike LV GLS, PALS was significantly reduced in those with paroxysmal AF, and found that PALS <29% predicted paroxysmal AF with a specificity of 76% and a negative predictive value of 93% (41).

Therefore, the use of PALS in patients with AF or with previous cryptogenetic stroke would provide further insights into the existence of thromboembolic risk related to AF, and thus to the need of anticoagulation therapy (42).

Valvular heart disease

The current guidelines for the management of valvular heart disease (VHD) recommend surgical treatment of VHD only for symptomatic patients, or in absence of symptoms, only in case of significant cardiac damage, which often reveals irreversible. Therefore, in the last years scientific interest has been growing on the research of reliable indices of subtle myocardial damage in order to identify the optimal surgical timing for VHD, particularly in mitral regurgitation (MR) and aortic stenosis (AS), also in light of the advances in percutaneous treatment. LA strain was one of the parameters that emerged from recent studies with this aim.

Mitral regurgitation

LA strain showed great results in studies evaluating MR severity and prognosis, also overcoming GLS (43, 44), probably because LA is the chamber directly affected by the chronic volume overload deriving from worsening MR. PALS had a correlation with current criteria for mitral surgery: symptoms, AF, and the development of PH (45); moreover, it was able to predict postoperative LA reverse remodeling and clinical outcome i.e. survival, AF and postoperative functional capacity (46) not only in patients with severe MR, but also in lower

grades of the disease (47, 48). Also, PALS during exercise has shown to be associated with survival and HF hospitalization in a cohort of 196 patients with primary or secondary MR (49). Therefore, a standardized use of LA strain would allow to add it as a criterion to provide early surgery and improving outcome of patients with MR.

Aortic stenosis

In patients with severe AS, the resulting LV outflow tract obstruction causes a chronic increase in LV filling pressures with LA dilatation and dysfunction as long-term consequence. Since LA functional impairment appears to occur earlier than LA dilatation in AS, PALS could be used to identify early damage also in this setting.

In fact, PALS showed to be correlated with prognosis in patients with several degrees of AS (50, 51), and with the development of post-operative AF caused by fibrosis, increased myocardial stiffness, and altered relaxation (52), also regardless of pre-existing LA dilatation (53). Also, LA strain was the major determinant of PH in patients with severe AS and preserved LVEF (54) and a marker of LA remodeling after transcatheter aortic valve replacement (55), suggesting that a serial evaluation of LA function in these patients could help providing early surgical treatment also in AS before the development of PH and irreversible LA damage.

Coronary artery disease

Although the target chamber for the evaluation of CAD is the LV, also the other cardiac chambers could be either directly affected by ischemic cardiac injury or involved in post-ischemic acute or chronic HF, therefore it could be useful to apply STE to characterize early myocardial damage also in these patients. Particularly, in a cohort of patients with acute myocardial infarction (AMI) undergoing invasive coronary angiography, PALS revealed to be lower in patients with a circumflex artery as culprit lesion, as expectable, since it is responsible for LA perfusion. Moreover, PALS and PACS were significantly reduced in patients with stable CAD and SYNTAX score ≥ 33 (56). Antoni et al. investigated the prognostic value of LA strain in AMI, founding that it was related to clinical outcome in a cohort of patients with AMI undergoing percutaneous coronary intervention (57).

Hypertrophic cardiomyopathy

Due to the prevalent component of diastolic dysfunction in the failing hearts affected by hypertrophic cardiomyopathy (HCM), some authors sought to determine the potential role of LA strain for the evaluation of these patients. Initial evidence showed that HCM patients un-

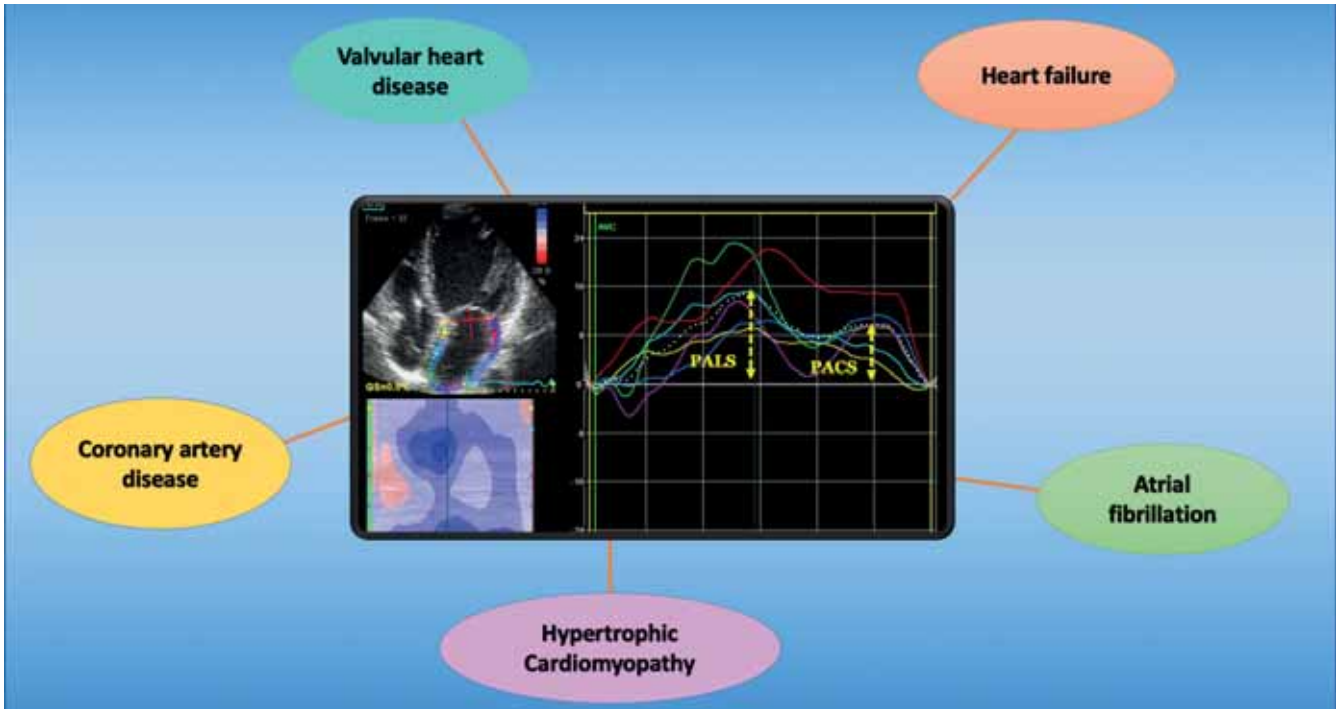


FIGURE 2. Left atrial strain importance as additional tool in different clinical settings

dergo progressive LA remodeling and dysfunction that could be reliably detected by STE in its early phase (58, 59). Interestingly, Fujimoto et al. conducted a prognostic study in patients with CMR diagnosis of HCM, founding that PALS and PACS were both significantly impaired in HCM patients, however, the loss of LA active function in particular, assessed by a reduction of PACS <20.3% was able to stratify the risk of increased cardiac events (AF, mortality, HF hospitalization) in these patients with HCM (P=0.01) (60).

Conclusions

Although some limitation of LA strain by STE should be considered, such as its loading- and image quality-dependance, and the lack of disease-specific reference cut-off values for reference, the road for its standardized use has been found (1, 2) and the plenty of available evidence suggest its use as an additional tool to improve the diagnostic and prognostic algorithms and improve the choices on therapeutic management in different clinical settings (Fig. 2).

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