REVIEW ARTICLE

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# Detection of atrial fibrosis using echocardiographic strain: a new pathway

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## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of approximately 3% in adults, which is likely to increase with age, making its prevention and appropriate management essential factors[1]. AF is independently associated with a 1.5- to 2-fold increase in morbidity and mortality risk by all causes in the population in general[2,3].

Inflammation has been associated with the pathophysiology of AF and several pathological processes, such as oxidative stress and apoptosis. Inflammation in the atrium seems to be related to the emergence of AF, which is part of the fibrosis pathophysiology, and contributes to its appearance in the left atrium (LA)[4].

Diseases such as ischemic cardiomyopathy, cardiac valvulopathy, and cardiac insufficiency are associated with the dilation of the LA and an increased risk of developing AF[1-3,5]. The enlargement of the LA was initially studied with the aim of evaluating its relationship with AF, because an atrium with a larger volume is associated with a higher risk of AF, mainly in the elderly[6]. Recently, a significant association of peak atrial longitudinal strain (PALS) of the LA and the progression of AF was demonstrated[4].

In addition to other cardiovascular diseases, the high prevalence of AF represents an important epidemiological, clinical, and economic concern. The identification of echocardiographic parameters, with the objective of an early detection of atrial alterations in structure and function, becomes a valuable tool that can contribute to the identification of patients with a higher risk or a worse prognosis in face of AF[6]. The increase in the LA fibrosis can predict the prognosis after ablation[7].

Echocardiography is the most used tool to evaluate atrial size and function[7]. As a diagnostic method, speckle tracking echocardiography (STE) has been used for the detection of atrial fibrosis and it presents good perspectives for its use in the routine of clinical practice[8]. STE is an advanced imaging technique that allows the assessment of the deformations of the LA reservoir function, potentially caused by the decrease in complacency due to atrial fibrosis[7].

The objective of this review was to investigate the usefulness of STE as an atrial fibrosis marker in patients with AF.

## METHODS

This study is an integrative literature review carried out in six steps:

1) identification of the subject and selection of the research question;
2) definition of inclusion and exclusion criteria;
3) search for the studies and extraction of results;
4) assessment of the studies;
5) interpretation of the results; and
6) knowledge summarizing[9].

The research question was elaborated based on PICO search strategy (P – population: patients with FA; I – interest: atrial fibrosis; Co – context: STE for the assessment of atrial fibrosis). It resulted in the following guiding question: Are

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the parameters assessed in the STE useful as markers for atrial fibrosis in patients with AF?

The inclusion criteria were as follows: articles which the objectives aimed at discussing the use of STE as a marker for atrial fibrosis in patients with AF, of the type clinical studies, observational studies, and meta-analysis or systematic reviews that were published between 2011 and 2021. We excluded articles targeting the pediatric population, other review methods, studies that did not approach atrial fibrosis assessed by STE, books, monographs, dissertations, thesis, and editorials. Databases used were as follows: PubMed, ScienceDirect, *Literatura Latino Americana y del Caribe em Ciências de La Salud* (LILACS), *Medical Literature Analysis and Retrieval System Online* (MEDLINE), and *Portal da Biblioteca Virtual de Saúde* (BVS).

Sampling was carried out by survey and analysis of the publications using the descriptors selected from *Descritores em Ciências da Saúde* (DeCS, http://desc.bvs.br): Atrial fibrillation, Atrial fibrosis, Strain, Speckle tracking, and their respective translations to Portuguese language, with the crossing performed by the Boolean operator "*and*."

Initially, titles and abstracts were read by two independent researchers and each researcher registered the decision to include or not the study assessed (step 1). Divergent cases were submitted to a third researcher for evaluation (step 2). Subsequently, articles included by the three researchers were fully read in order to search for the study question (step 3).

The assessment with regard to the Level of Evidence (LE) followed the guidelines of the *Oxford Centre for Evidence-Based Medicine*[10,11] as shown in Table 1. Information extracted was descriptive and directly related to the study question (Tables 1 and 2).

The search retrieved 76 studies, which were reviewed according to the eligibility criteria, and 6 articles[5,8,12-15] were selected, as shown in Figure 1.

## RESULTS

In total, six articles fulfilled the eligibility criteria and answered the research question. Figure 1 describes the flow for the identification, selection, eligibility, and inclusion of studies.

The articles were analyzed regarding their quality and categorized by the degree of recommendation and LE[11]. Two studies[8,12] were classified as recommendation grade A (high), two studies[13,14] were grade B (moderate), and two studies were grade C (low)[5,15]. With regard to the type of study, five articles were primary research and only one was a review (Table 1).

## DISCUSSION

Atrial fibrosis causes conduction disturbances and contributes to the atrial remodeling. A recent study suggests that cardiomyocytes can release inflammatory cells, for instance, cardiac fibroblasts that are responsible for the fibrous tissue formation. They are activated by cytokines, growth factors, and adipokines, among others, being related to inflammatory diseases that can be aggravated when associated with comorbidities. Therefore, atrial inflammation, even the subclinical type, can contribute to the appearance of fibrosis[16].

In AF, an important LA remodeling occurs in addition to collagen deposition in the interstice. It causes fibrosis and consequently alterations in the electric conduction that tend to increase progressively, favoring the conversion to permanent AF[7]. Atrial

**Table 1.** Summary of studies according to author, year, level of evidence, method, and objective.

| Author and year/ level of evidence and recommendation | Method | Objective |
|---|---|---|
| Nielsen et al., 2020[8]/1A | Systematic review and meta-analysis | Investigate whether the peak atrial longitudinal strain assessed by STE can predict AF recurrence after treatment with radiofrequency ablation. |
| Laish-Farkash et al., 2020[12]/1A | Clinical trial | Investigate the relationship between LA remodeling using STE and high-density voltage mapping in AF patients |
| Moreno-Ruiz et al., 2019[13]/2B | Cohort prospective | Evaluate the predictive value of PALS for arrhythmia recurrence after electrical cardioversion in persistent and long-standing persistent nonvalvular atrial fibrillation using STE |
| Leung et al., 2018[14]/3B | Case–control retrospective | Investigate the relationship between LA reservoir strain and total atrial conduction time using STE |
| Pilichowska et al., 2018[5]/2C | Observational prospective | Evaluate the relationship between LA fibrosis derived from STE parameters as well as biomarkers of fibrosis in patients with AF |
| Watanabe et al., 2015[15]/2C | Observational retrospective | Clarify the relationship between LA mechanical function STE and LA electrical remodeling using an electroanatomic mapping system and to estimate AF substrate |

STE: speckle tracking echocardiography; AF: atrial fibrillation; LA: left atrium; PALS: peak atrial longitudinal strain.

**Table 2.** Summary of studies according to the number of patients and main results.

| Number of patients | Main results |
|---|---|
| 1,025[8] | – Patients with lower values of peak atrial longitudinal strain (PALS) are associated with an increased risk of AF recurrence.<br>– PALS is considered a significant predictor of AF recurrence after radiofrequency ablation<br>– PALS provides information regarding the expected response to ablation, which can be of use to select patients for optimal treatment. |
| 42[12] | – Low-voltage zones ≥5% present a negative association with the LA reservoir phase, which suggests significant remodeling and fibrosis (p<0.01). |
| 131[13] | – Atria from patients with AF of shorter evolution time are more compliant due to a lower degree of fibrosis when considering the difference in PALS values (p<0.001).<br>– Patients with AF recurrence presented more fibrosis (remodeling) by lower global atrial longitudinal deformation (p<0.001). |
| 602[14] | – Fibrosis is considered a primary driver of AF, resulting in the formation of micro reentry circuits that may initiate and perpetuate the atrial arrhythmia.<br>– Remodeling of the atrial substrate and increasing fibrosis may reduce LA compliance (p<0.001).<br>– LA compliance is impaired in AF, and together with the significant negative relation with total atrial activation time, suggests that these changes may be due to atrial fibrosis (p<0.001). |
| 66[5] | – Left atrial diastolic (p<0.001) and volume (p<0.002) parameters correlate well with the extent of LA fibrosis, assessed by invasive methods.<br>– STE may be useful in the noninvasive assessment of LA fibrosis (p<0.001). |
| 52[15] | – Dyssynchrony was prominent in AF patients with low-voltage zones in the LA (p<0.001). |

AF: atrial fibrillation; LA: left atrium; PALS: peak atrial longitudinal strain.

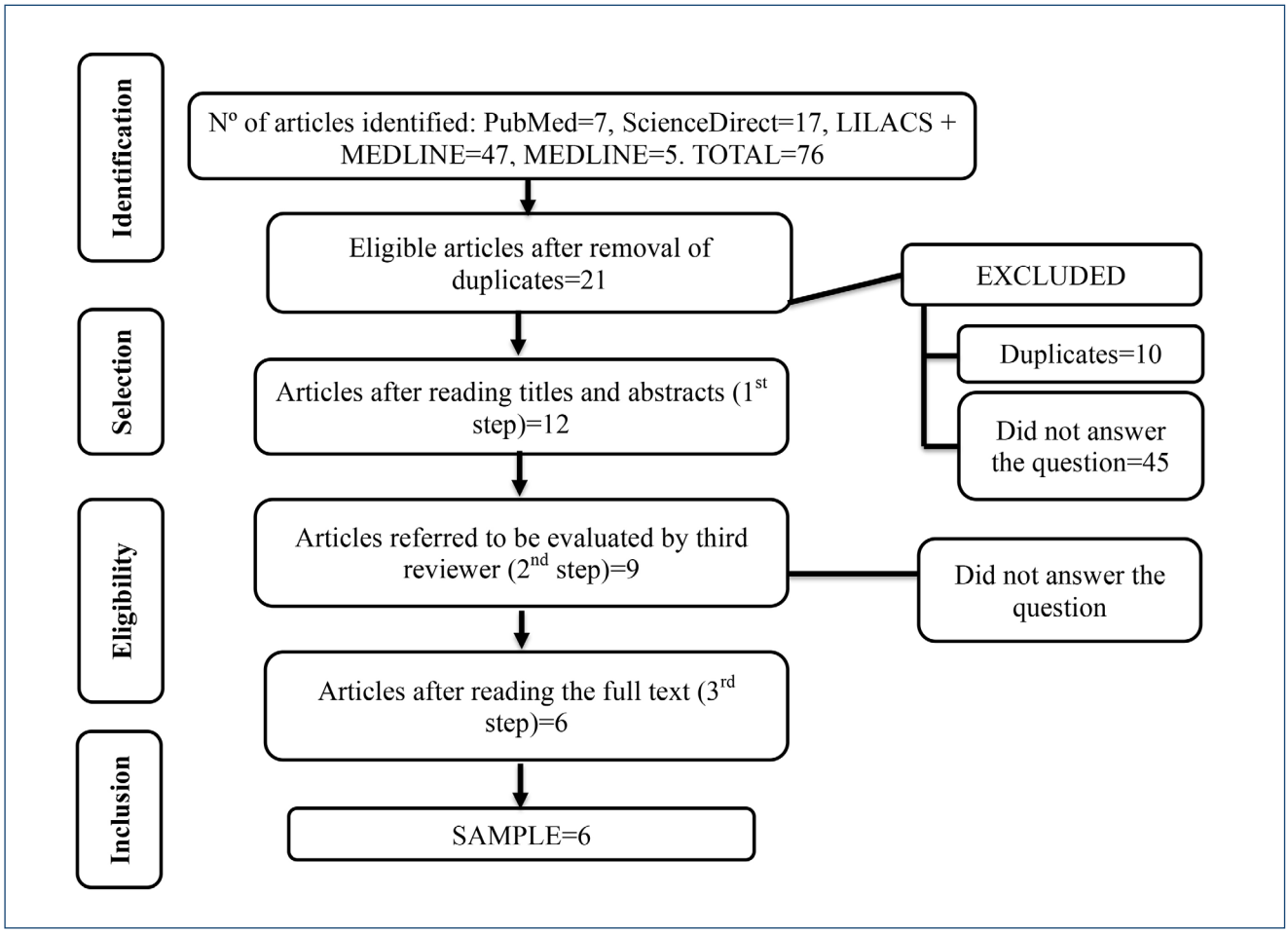


**Figure 1.** Flow diagram of search strategy results and study selection.

fibrosis is a result of an atrial structural remodeling and acts as a substrate for AF, playing an important role in the disease[17].

In the long run, fibrosis is an important factor causing mechanic damages[17]. It can be caused and/or aggravated by several diseases or clinical conditions, among them, AF itself, in which a rapid atrial myocyte depolarization occurs and contributes to the fibrosis[18]. Thus, AF may be a consequence of the fibrosis and can be aggravated by arrhythmia, leading to a chronic process.

Atrial fibroblast remodeling prevention is essential, and evidence shows how important it is to detect the fibrosis stage because it can help in the therapeutic decision for these patients[6]. Therefore, it has been suggested that the assessment of atrial fibrosis presence as early as possible is crucial.

Markers can be used in the clinical practice for the prediction, diagnosis, and prognosis, in addition to allowing the monitoring of the response to the treatments offered. It is noteworthy that markers should be used together with a critical analysis and always interpreted in the light of clinical data[19].

In the context of fibrosis and AF, the possibility of imaging examinations to identify and/or predict atrial fibrosis has emerged. STE is used to assess/track "stains" that are suggestive of myocardial deformation. In AF, the peak atrial longitudinal strain (PALS) measured at the end of reservoir phase is an important deformation parameter, since it depends essentially in the atrial compliance[6].

Nielsen et al.[8] suggest that PALS can be considered a superior predictor of AF recurrence after ablation because it reflects the compliance of the LA wall as well as atrial fibrosis and characterization and quantification of myocardial deformation (weighted mean difference [WMD]: 6.57, 95%CI −8.49 to −4.65, p<0.001).

The authors also defined an ideal PALS value to predict AF recurrence (<12.8%, range 10–18.8%), with a weighted mean sensitivity of 80% (range 74–86%) and specificity 87% (range 71–98%). The optimal value for PALS to predict the maintenance of sinus rhythm is >20.5% (range 15–30%), with a weighted mean sensitivity of 76% (range 56–97%) and specificity of 81% (range 58–100%)[8].

In a clinical trial carried out by Laish-Farkash et al.[12], the relationship between LA remodeling assessed by STE and high-density voltage mapping in patients with AF was investigated. The study showed low-voltage zones ≥5% were negatively correlated with LA reservoir phase, suggesting significant remodeling and fibrosis (p<0.01).

Evaluation of the fibrosis extension in the LA guided by magnetic resonance imaging may influence the decision-making process in the management of patients with AF, mainly by guiding the selection of patients considered adequate candidates for ablation and predicting the probability post-ablation of maintaining sinus rhythm[12]. This examination is an established tool for obtaining images of myocardial fibrosis; however, it is highly costly, requires experience for the appropriate image acquisition and analysis[7], cannot be performed in all patients (for instance, patients with chronic kidney insufficiency), and is not available in most hospitals in developing countries[6].

Moreno-Luiz et al.[13] carried out a study with the objective of assessing PALS predictive value in patients with persistent and long-standing persistent AF submitted to electrical cardioversion. The authors demonstrated that atria from patients with shorter evolution time AF are more compliant due to a lower degree of fibrosis when considering PALS values (p<0.001) and that patients with AF recurrence presented more fibrosis by lower global atrial longitudinal deformation (p<0.001).

Leung et al.[14] found out that, compared with controls, patients with paroxysmal AF and patients with persistent AF presented a progressive reduction in the LA reservoir deformation (36.9±11.6%, 29.8±13.4%, 24.2±12.3%, respectively, p<0.001). The study also demonstrated that both the presence and burden of AF were associated with morphofunctional abnormalities of the LA, represented by larger LA volumes, longer total atrial activation time, and more impaired LA reservoir strain.

Pilichowska et al.[7] reported that LA diastolic parameters derived from STE correlate well with the extent of LA fibrosis. Hence, they suggested STE could be useful in the noninvasive assessment of LA fibrosis and selection of candidates for ablation. In diagnosis and determining interventional AF treatment, the need for precise LA evaluation is highlighted because the LA wall properties are associated with the effectiveness of the treatment.

Watanabe et al.[15] suggested that LA dyssynchrony was especially pronounced in patients with paroxysmal AF who had a low-voltage zone in their LA (p<0.001). This alteration may be a result of the regional fibrosis of the LA myocardial tissue. Regional fibrosis may lead to the heterogeneity of LA wall, result in dyssynchrony, and also cause the local conduction delay by separating atrial myocytes.

Anamnesis, physical examination, and imaging examinations already established in the literature, associated with new examinations of atrial fibrosis markers, can represent the future of patients' assessment with or in risk of developing AF. The reason is that this strategy presents a potential to guide a more individualized and appropriate therapeutic choice for this disease, which represents a public health concern all over the world. In that regard, speckle tracking assessed by the echocardiography is an atrial fibrosis marker candidate useful for the selection of patients suitable for ablation.

## CONCLUSION

Atrial fibrosis is considered a substrate for AF, especially in patients who are in an advanced stage of the disease. The use of markers is an important tool in the search for new means of disease management. In our review, we confirmed that STE can be considered a predictive, diagnostic, and prognostic marker for atrial fibrosis in patients with AF.

## AUTHORS' CONTRIBUTIONS

**MMBMS:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **DCO:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **JVBC:** Data curation. **ATX:** Data curation. **LRC:** Data curation. **DJFN:** Data curation. **JMDC:** Writing – original draft, Writing – review & editing. **LRSV:** Writing – original draft, Writing – review & editing. **DCSF:** Writing – original draft, Writing – review & editing.

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