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REVIEW

Progress in the Study of the Left Atrial Function Index in Cardiovascular Disease: A Literature Review

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Abstract

Some studies have shown that left ventricular structure and function play an important role in the risk stratification and prognosis of cardiovascular disease. The clinical application of left atrial function in cardiovascular disease has gradually attracted attention in the cardiovascular field. There are many traditional methods to evaluate left atrial function. Left atrial function related indexes measured by echocardiography has been identified as a powerful predictor of cardiovascular disease in recent years, but they have some limitations. The left atrial function index has been found to evaluate left atrial function more effectively than traditional parameters. Furthermore, it is a valuable predictor of the risk stratification and prognosis in patients with clinical cardiovascular disease such as heart failure, atrial fibrillation, hypertension, and coronary heart disease.

Keywords: Left atrial function index; Left atrial function; Cardiovascular disease

Introduction

It is well known that the atria play a key role in the physiological equilibrium of the heart. In recent decades, research efforts have focused on the evaluation of atrial function [1–3]. There are many ultrasound indicators to evaluate left atrial function, among which a special indicator, the left atrial function index (LAFI), has been increasingly found in some studies to be of additional value for cardiovascular disease risk stratification and prognosis.

Background and Origin

Left atrial function can reflect the changes in left ventricular function to some extent, especially those of left ventricular diastolic function [2, 3]. The left atrium plays an important role in maintaining cardiac physiological function, which is manifested mainly in the following three ways: (1) during left ventricular systole, the left atrium receives and

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stores blood from the pulmonary vein; (2) during the early period of left ventricular diastole, the left atrium acts as a lumen to drain pulmonary venous blood to the left ventricle; and (3) at the end of left ventricular diastole, the left atrium acts as an output pump to supply blood actively to the left ventricle [1, 2]. When left ventricular diastolic function begins to decrease, left atrial emptying capacity decreases, while the left atrial storage function and active systolic function can compensate. With further limitation of left ventricular diastolic function, or decrease of left ventricular systolic function, the left ventricular filling pressure increases, and left atrial function gradually enters the decompensation stage; that is, left atrial function decreases and left atrial volume increases.

The clinical usefulness and potential prognostic value of LA function assessment have received attention, some parameters related to left atrial function have a potential predictive value for the risk stratification and prognosis of cardiovascular disease [2, 3]; however, they also have some limitations. First of all, because left atrial function is affected by the structure of the left atrium and left ventricular function, some parameters cannot fully reflect the overall functional state of the left atrium, such as left atrial ejection fraction (LAEF) [4]. Secondly, myocardial strain (rate) is a powerful indicator for sensitive assessment of left atrial function; however, because of the variability and heterogeneity of strain parameters, its reference value cannot be accurately estimated [5]. In addition, parameters such as the peak A wave velocity of transmitral flow obtained by pulsed wave Doppler imaging (A value) and the A′ velocity obtained by Doppler tissue imaging (A′ value) during atrial systole are easily affected by non-sinus rhythm factors. As a consequence, the results obtained in patients with atrial fibrillation (AF) are not necessarily accurate.

So are there other parameters related to left atrial function that can be better assessed? Sardana et al. [6] found that the LAFI is a comprehensive, sensitive, and accurate indicator to evaluate left atrial function, and the ultrasonographic indicators related to left ventricular remodeling, such as the left ventricular ejection fraction and left ventricular end-systolic volume (LVESV), as well as AF and cardiovascular events, are closely correlated [6]. But there is a lack of more clinical research data, and this index has not been widely used in clinical practice.

Definition and Characteristics

Tormas et al. [7] formally proposed the concept of the LAFI in 2008. It is a ratio associated with left atrial structure, left atrial function, and left ventricular function. The formula for the LAFI is similar to the formula used to calculate the atrial index: transmitral velocity-time integral of E and A waves (VTI) total × the left atrial ejection fraction/left atrial maximum area [8]. Namely, it is calculated from LAEF, the left atrial outflow tract VTI (LAOT-VTI), and the left atrial maximum volume index (LAESVI) as follows [7]:

$$\text{LAFI} = \frac{\text{LAEF} \times \text{LAOT-VTI}}{\text{LAESVI}}.$$

LAEF represents the left atrial emptying capacity and reflects mainly left atrial function. LAEF is calculated from the left atrial end-diastolic volume (LAEDV) and the left atrial end-systolic volume (LAESV) as follows:

$$\text{LAEF} = \frac{\text{LAESV} - \text{LAEDV}}{\text{LAESV}}$$

The left ventricular outflow tract VTI (LVOT-VTI) is similar to the left ventricular output, and reflects left ventricular function to some extent. The LVOT-VTI is calculated from the LVEDV, the LVESV, and the left ventricular outflow tract cross-sectional area (CSA) as follows:

$$\text{LVOT-VTI} = \frac{\text{LVESV} - \text{LVEDV}}{\text{CSA}}.$$

The LAESVI represents the left atrial reserve capacity and reflects the anatomical structure of the left atrium, and is calculated from the LAESV and body surface area (BSA) as follows:

$$\text{LAESVI} = \frac{\text{LAESV}}{\text{BSA}}.$$

Including LAEF and the LAESVI in the formula provides comprehensive information about the anatomical structure and function of the left atrium. In addition, the LVOT-VTI is included in the formula, which can reduce the influence of the left ventricle on left atrial function. Therefore, the LAFI can comprehensively evaluate left atrial function, and indirectly reflects left atrial remodeling and left ventricular function to some extent. Thus, the LAFI appears to be a very sensitive but not very specific marker of left atrial and left ventricular diastolic dysfunction [9]. Another important advantage of this measurement is that it is rhythm independent, while some ultrasound parameters for evaluating left atrial function, such as the A value, the A′ value, and its VTI, are inaccurate in non-sinus rhythms, which limits their efficacy in evaluating left atrial function in AF. A possible reason is that the LAFI depends on the left atrial emptying fraction, which provides an estimation of atrial function, but is not tightly related to atrial contraction. Experts suggested that the LAFI was associated with AF and cardiovascular events in the Framingham Offspring Study [10]. As early as 2005, it was suggested that the LAFI might provide clues to the outcome of cardiovascular disease [11]. Consequently, combined with the above-mentioned characteristics, the LAFI can provide a more accurate predictive value for the clinical risk stratification and prognosis of some cardiovascular diseases.

Application in Cardiovascular Diseases

Left Atrial Function Index and Heart Failure

It has been found that left atrial function is related to the readmission and survival rates of patients with heart failure (HF), and has more predictive value than does the left atrial volume [12]. A study of 357 patients with HF with preserved left ventricular ejection fraction (HFpEF) treated with aldosterone antagonists found that 91 patients (25.5%) with HFpEF experienced cardiovascular death, rehospitalization for HF, or sudden death. After adjustment for clinical confounding factors, the correlation between the parameters of left atrial function and readmission for HF is significant, and confirms that left atrial function in patients with HFpEF can predict the risk stratification and prognosis of HF to some extent [13]. Left atrial dysfunction may simply be a consequence of other pathophysiologic mechanisms that cause HF. On the basis that the LAFI is sensitive to changes in left atrial function, Welles et al. [14] further found that left atrial function quantified by the LAFI is inversely related to the hospitalization rate of HFpEF patients with coronary heart disease (CHD) over a median follow-up of 7.9 years. Even after adjustment for the echocardiographic covariates, this correlation existed independently. Additionally, regardless of whether improvement of left atrial function could affect outcomes, the LAFI provides prognostic value that is incremental to clinical risk factors and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels, and therefore may be useful in risk stratification to identify patients with preserved baseline ejection fraction who are at high risk of hospitalization for HF. In addition, the LAFI combined with NT-proBNP levels might be better to predict the risk of clinical cardiovascular adverse events in HFpEF patients.

The LAFI is of clinical value not only in patients with HFpEF, but also plays an important role in HF with reduced left ventricular ejection fraction (HFrEF). Sargento et al. [15] studied 203 outpatients with HFrEF. In four different multivariate models that included different confounding factors, the LAFI was compared with its separate components (LAEF and LAESVI). It was found that the LAFI was the only effective predictor of survival. Moreover, the LAFI was found to be significantly correlated with some clinical indexes and echocardiographic parameters, including New York Heart Association grade, NT-proBNP levels, left ventricular global strain rate, and atrial strain rate. In addition, a high LAFI is a strong predictor of survival in patients with HFrEF, while a low LAFI is a strong predictor of death in patients with HFrEF. An LAFI less than 24.5 is a strong predictor of the risk of death in patients with HF. More interestingly, the LAFI was superior to each of its individual components in predicting the outcomes, including survival. This means that the association between the anatomical and functional features of the left atrium and the inclusion of left ventricular systolic function in the index provide a better prediction of survival compared with the individual elements. Thus, the LAFI can effectively predict long-term survival and mortality in patients with HFrEF, showing that its use should be associated with current measurements for a more tailored risk stratification of patients with HFrEF [15].

On the basis of the above-mentioned studies, the LAFI has predictive value in clinical risk stratification and prognosis of HF. Of course, all these findings need to be confirmed in larger cohorts of patients and in different clinical settings, particularly HFpEF. However, the great results obtained so far and the easily understandable potential of a complete parameter let us hope that, maybe, we can find a better alternative to assess the outcome of HF.

Left Atrial Function Index and Atrial Fibrillation

AF is increasingly being recognized as important in the diagnosis or prognosis of cardiovascular disease. Left atrial functional and structural remodeling are important in the maintenance and progression of AF [16]. Bertelsen et al. [17] found that left atrial function is more likely to predict the risk of cardiovascular death or hospitalization for HF in patients with AF than is left atrial structure. Left atrial function is usually difficult to evaluate in non-sinus rhythm, and the related index of left atrial function is often irregular, leading to irregularities such as large dispersion and poor comparability. The LAFI has rhythm independence, and can more accurately evaluate left atrial function, reflect left atrial structural and functional remodeling, and predict the risk of major adverse events, such as stroke and HF, in patients with AF. As the study expected, AF was far more common among participants in the lowest quartile of the LAFI compared with those in the higher quartiles of the LAFI [15]. This is consistent with the previous finding that the LAFI is low in individuals with AF and increases on successful cardioversion to sinus rhythm [7].

The LAFI is reportedly a possible predictor of hospitalization for HF and AF. Furthermore, the effects of catheter ablation on the LAFI have been reported. The LAFI might be used to evaluate the improvement of left atrial function and structure after radio-frequency catheter ablation (RFCA) in patients with AF. RFCA is an effective treatment for AF and can reportedly improve the postoperative function and structure of the left atrium [18]. A study of patients with paroxysmal AF found that left atrial function decreased briefly after RFCA and then gradually improved, while the LAFI decreased briefly 3 days after RFCA and increased steadily by 1, 3, and 6 months after RFCA. Nagase et al. [19] studied 55 patients with AF who underwent catheter ablation and found that left atrial volume began to decrease 1 month after catheter ablation, and reached a stable state 3–6 months later. The maximum left atrial volume 12 months after catheter ablation was significantly lower than that preoperatively (maximum left atrial volume preoperatively vs. postoperatively, 87.3 ± 28.4 mL vs. 72.4 ± 28.3 mL; $P=0.0001$), while the LAFI began to increase at 1 month after catheter ablation and reached a stable level at 3–6 months. In patients with maximum left atrial volume exceeding 63.5 mL, there was no significant increase in the LAFI and it was significantly lower than the normal range. Studies have confirmed that the LAFI can accurately reflect the improvement of left atrial structure after catheter ablation [19]. Therefore, this means that the LAFI may have important value in assessing the improvement of left atrial function and structure after catheter ablation.

Besides, the LAFI can predict the recurrence of AF after catheter ablation. Sardana et al. [20] showed that 78 patients with AF (46%) had recurrence of late AF after catheter ablation, mainly in patients with a low LAFI. This was still associated with recurrence of AF after catheter ablation in logistic regression analysis adjusted for factors known to be associated with AF [odds ratio 0.04 (0.01–0.67), $P=0.02$]. The study also found that the predictive ability of the LAFI for AF recurrence after catheter ablation was slightly better than was the $CHADS_2$ score (congestive HF, hypertension, age 75 years or older, diabetes mellitus, stroke), while in patients with persistent AF, the LAFI was significantly better at predicting AF recurrence after catheter ablation than was the $CHADS_2$ score. The relationship of mechanical remodeling of LA with recurrence has been studied extensively with several advanced imaging techniques, and mechanical atrial dysfunction is associated with increased risk of AF recurrence after CA. LAFI, an echocardiographic measure of atrial mechanical function, reflects atrial substrate better than the measures of atrial size alone and its association with AF recurrence is independent of atrial size. To sum up the above studies, LAFI is a clinically useful discriminator for AF recurrence and left atrial mechanical function changes after catheter ablation when considering catheter ablation as a therapeutic option for symptomatic patients with AF.

Left Atrial Function Index and Hypertension

There has been no study on the correlation between the LAFI and hypertension, but from the pathophysiology of hypertension, the LAFI can be used for the risk stratification and prognosis of hypertension by reflecting left atrial function and structure. In hypertensive patients with left ventricular hypertrophy and decreased left ventricular compliance, left atrial active emptying function decreases. According to the Frank-Starling mechanism, a compensatory expansion of left atrial structure and a slight increase of left atrial systolic function were observed. With the increased left ventricular filling pressure, the left atrial functional structure was decompensated, which was characterized by obvious left atrial enlargement and decreased left atrial function [21].

Therefore, alterations in left atrial and left ventricular function have been documented in hypertensive patients. The correlation of left atrial functional changes with left ventricular functional changes in hypertensive patients has been further confirmed by Fung et al. [22]. Left atrial function and structure play an important role in the maintenance and progression of hypertension and can predict the risk of clinical adverse cardiovascular events, such as AF or HF in patients with hypertension [23].

On the basis of the significance of left atrial function and structure in patients with hypertension, the LAFI can predict the possible impact of left atrial functional and structural changes on cardiac function in patients with hypertension, which is significantly correlated for the effective prevention and treatment of hypertension, and the prevention of complications caused by hypertension. However, the direct correlation of the LAFI with hypertension has not been established, and evaluation of the value of the LAFI in hypertensive patients should be explored in the future.

Left Atrial Function Index and Coronary Heart Disease

The LAFI can independently predict the rate of hospitalization for HF in patients with stable CHD with ejection fraction greater than 50%, and a decreased LAFI predicts an increased risk of adverse cardiac events [14]. In early CHD, insufficient coronary perfusion, chronic myocardial ischemia and hypoxia, decreased left ventricular regional diastolic function, and increased left ventricular filling pressure lead to decreased left atrial function. Impaired left atrial function is one of the signs of myocardial ischemia. In 2014, Wong et al. [24] selected 983 patients with stable CHD to continue the above-mentioned study. Left atrial function was quantified by the LAFI. The association between the LAFI and ischemic stroke or transient ischemic attack (TIA) was evaluated by the Cox proportional hazards model. During an average follow-up period of 7.1 years, the LAFI was negatively correlated with the risk of ischemic stroke or TIA in patients with CHD. Patients with the lowest LAFI had more than three times the risk of ischemic stroke or TIA than patients with the highest LAFI. This proves that left atrial dysfunction is an independent risk factor for stroke or TIA, even in patients without baseline AF. The LAFI is the strongest predictor of ischemic stroke or TIA in patients with CHD among measured echocardiographic indexes of left atrial function and left atrial volume, and even has a certain predictive value for the risk stratification and prognosis of CHD. The relation between left atrial dysfunction and ischemic stroke may be explained through AF acting as either a confounder or a mediator. Previous studies showed that the LAFI can predict left atrial dysfunction in advance and increase the risk value of predicting AF.

Modin et al. [25] found that the LAESVI could not reflect the changes of cardiac function directly after acute myocardial infarction, but the parameters related to left atrial function were more closely related to changes of the left ventricular filling pressure than those related to left atrial structure, and could more sensitively reflect the changes of the left ventricular hemodynamics directly after acute myocardial infarction. This is possibly because the variability of the atrium is high directly after acute myocardial infarction, and the structure of the left atrium cannot accurately reflect the short-term decline of cardiac function after acute myocardial infarction, so the LAFI may predict the clinical risk stratification and prognosis of acute myocardial infarction by quantifying left atrial function. However, there is no clear research locally or globally, and this indicates an important future research direction.

Limitations and Expectations

The application of the LAFI provides more reference value for clinicians to better evaluate cardiac function status. However, compared with the commonly used evaluation indicators of left atrial function, the LAFI has not been widely used in the clinical or the research environment. A possible reason is that currently there is no optimized ultrasound software to directly measure the LAFI, so measurement of the LAFI needs to be done indirectly through formulas and other traditional parameters, which increases the time needed. Secondly, focusing on clinical study results only in certain and single cardiovascular diseases results in lack of deeper analysis for complicated real applications. On the one hand, studies have found that left atrial remodeling, including myocardial fibrosis, functional and electrical remodeling, has important potential value in predicting adverse cardiovascular events [26]. On the other hand, LAFI is also a sensitive marker reflecting pathological remodeling of the left atrium [6]. In the future, the association between LAFI and myocardial fibrosis related parameters or electrophysiological parameters can be further studied to evaluate the overall remodeling of the left atrium and to increase the added value of risk stratification and prognosis assessment of cardiovascular disease.

Conclusions

Currently, there are many parameters related to left atrial function in the evaluation of cardiovascular disease, and they have both advantages and limitations in clinical application. The LAFI combines many factors to evaluate left atrial function accurately, and reflects left atrial remodeling and left ventricular diastolic function to a certain extent. It is a comprehensive index with heart rhythm independence, not affected by non-sinus rhythm factors. In brief, it has important clinical application value for the occurrence, development, risk stratification, and prognostic evaluation of clinical cardiovascular disease such as HF, AF, hypertension, and CHD. Despite partial limitations regarding its clinical application, the clinical application value of the LAFI is a new direction worth exploring.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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