



## Clinical Relevance of the Spectral Tissue Doppler E/e' Ratio in the Management of Patients with Atrial Fibrillation: A Comprehensive Review of the Literature

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### Abstract

Atrial fibrillation is the most common cardiac rhythm disorder observed in clinical practice. It carries high morbidity and mortality rates, primarily related to heart failure, stroke and death. Validation of noninvasive markers in the diagnosis of heart failure with preserved ejection fraction and risk stratification is relevant in this clinical setting. The spectral tissue Doppler-derived E/e' ratio is a simple and reproducible index, which has been validated in noninvasive assessment of left ventricular diastolic pressures, regardless of rhythm. Septal E/e' >11 is a good predictor of invasively determined left ventricular diastolic pressure >15 mmHg in patients with atrial fibrillation. Several studies have validated the clinical relevance of abnormal values for E/e' at rest and during exercise in the diagnosis and risk stratification of heart failure with preserved ejection fraction in patients with atrial fibrillation. Increased E/e' value is associated with adverse outcome (death, left atrial appendage thrombus, stroke and heart failure) in patients with atrial fibrillation and predicts arrhythmia recurrence after cardioversion and catheter ablation. In conclusion, E/e' by spectral tissue Doppler is clinically relevant in the clinical management of any patients with atrial fibrillation referred for transthoracic Doppler echocardiography.

### Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder observed in clinical practice. Despite advances in its diagnosis and therapeutic management, this condition remains one of the most common causes of cardiovascular morbidity and mortality, primarily related to stroke, heart failure and death<sup>[1]</sup>. This condition affects about 3% of the population over 20 years of age. Its prevalence is increasing, which is linked to a better detection of silent AF, the ageing of the population and an increase in diseases leading to its occurrence<sup>[1]</sup>. Experts recommendations issued in 2016 have highlighted the importance of cardiac imaging in the management of patients with AF<sup>[2]</sup>. Therefore, validation of simple, noninvasive parameters that can help diagnose concurrent heart failure, particularly with preserved ejection fraction, and predict outcome as well as arrhythmia recurrence, is of paramount importance in clinical setting.

Since the landmark studies by Nagueh et al.,<sup>[3]</sup> the clinical relevance of the spectral tissue Doppler E/e' ratio by transthoracic Doppler echocardiography has been definitely established. In particular, E/e' provides relevant information in noninvasive assessment of left

ventricular diastolic pressures and function, diagnosis and prognosis in outpatients, heart failure irrespective of ejection fraction, ischemic heart disease, hypertrophic cardiomyopathy, arterial hypertension and more broadly critically ill patients<sup>[4-24]</sup>. E/e' would therefore be to left ventricular diastolic function what ejection fraction is to systolic function in clinical practice<sup>[8,15]</sup>. Evidence has emerged that E/e' is also useful in patients with AF. The purpose of the present review is therefore to assess the diagnostic and prognostic relevance of the E/e' ratio in patients with AF.

### Relevance of E/e' in Noninvasive Assessment of Left Ventricular Diastolic Pressures in Patients with AF

The accuracy of E/e' in measuring left ventricular filling pressures is based on the fact that the mitral E velocity is primarily related to left atrial pressure and left ventricular relaxation in order of decreasing significance, and that the e' velocity by spectral tissue Doppler at the mitral annulus reflects left ventricular relaxation in patients with structural heart disease. The relation between these two velocities theoretically allows to overcome the influence of diastolic function and partially reflect left atrial pressure<sup>[7,22]</sup>. E/e' has been correlated to invasively determined left ventricular diastolic pressures and function in patients, irrespective of left ventricular ejection fraction<sup>[3,6-8,14,15,23]</sup>. E/e' is not accurate in assessing left ventricular diastolic pressures in healthy individuals and in patients with organic mitral valve disease and left ventricular wall motion abnormalities related to myocardial infarction, left bundle branch block, paced rhythm or coronary bypass<sup>[7]</sup>. Nevertheless, some studies have reported fair correlations between E/e' and invasively determined left ventricular diastolic

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pressures<sup>[25,26]</sup>.

One should keep in mind that accurately measuring invasive left ventricular filling pressures can be challenging in practice, which has been recently highlighted by fair correlations and wide scatter between pulmonary capillary wedge pressure and left ventricular end-diastolic pressure<sup>[27,28]</sup>. Last, this correlation, although statistically significant, allows only a semi-quantitative assessment of invasive left ventricular diastolic pressures. Several studies have specifically evaluated the reliability of E/e' in assessing left ventricular diastolic pressures in patients with AF. In the landmark study by Sohn et al. that included 27 consecutive patients with AF, in whom tissue Doppler velocities and invasive recordings were simultaneously assessed, e' measured at the septal side of mitral annulus was significantly and inversely correlated with tau ( $r = -0.51$ ,  $p < 0.01$ ), and septal E/e' was strongly correlated with invasive left ventricular diastolic pressure ( $r = 0.79$ ,  $p < 0.001$ )<sup>[29]</sup>. E/e' >11 had a sensitivity and specificity of 75 and 93%, respectively, in the prediction of invasive left ventricular diastolic pressure >15 mmHg. Currently, large evidence is that E/e' is significantly correlated with invasive left ventricular filling pressures in patients with AF ( $r = 0.404$  to  $0.765$ ,  $p < 0.05$ )<sup>[30-34]</sup>. Best results were obtained by measuring E and e' simultaneously<sup>[31,32]</sup>. However, this technology is not available on most current ultrasound machines, and several consecutive cycles must be recorded and averaged for E and e'.

### Relevance of E/e' in the diagnosis and prognosis of heart failure with preserved ejection fraction in patients with AF

Nearly half of patients with heart failure have preserved ejection fraction. The diagnosis is difficult in this setting and requires comprehensive assessment of left ventricular diastolic function by transthoracic Doppler echocardiography and/or catheterism. E/e' is clinically relevant in the diagnosis and risk stratification of heart failure with preserved ejection fraction, regardless of clinical presentation<sup>[7,8,15,20,21,35,36]</sup>. AF is a common comorbid condition in patients with heart failure and preserved ejection fraction<sup>[37]</sup>. Several studies have established the diagnostic relevance in this setting. A first work evaluated the value of E/e' in the diagnosis of heart failure with preserved ejection fraction in patients with AF with acute dyspnea<sup>[38]</sup>. Forty-one consecutive patients with left ventricular ejection fraction >50% were included, and septal E/e' >13 had a sensitivity and specificity of 82 and 89%, respectively, in the diagnosis of acute heart failure. Another study has confirmed these results in 73 patients with NYHA functional class I to IV<sup>[39]</sup>. Septal E/e' >11.7 had a sensitivity and specificity of 87 and 93%, respectively, in the diagnosis of heart failure with preserved ejection fraction (area under the ROC curve of 0.96) by using Framingham criteria as diagnostic reference. E/e' is inversely and independently correlated with functional capacity in patients with AF, confirming that an abnormal value for E/e' at rest and/or exercise strengthens the diagnosis of heart failure with preserved ejection fraction in patients with isolated exertional dyspnea and reduced exercise capacity<sup>[40-43]</sup>. In the study by Lee et al. that included 73 patients with AF, septal E/e' was an independent predictor of functional capacity ( $p = 0.03$ ), after adjusting for age ( $p = 0.006$ ) and heart rate ( $p = 0.03$ )<sup>[40]</sup>. In another work that included 50 patients with AF and preserved ejection fraction, the E/e' ratio (septal, lateral and average) was inversely correlated with the six-minute walk test and the quality of life questionnaire<sup>[41]</sup>. In another study

that included 94 patients with AF and preserved ejection fraction, multivariate analysis revealed that a resting lateral E/e' ratio >9 was independently associated with a decrease in peak VO<sub>2</sub> ( $p < 0.001$ ), after adjusting for age ( $p = 0.006$ ) and female sex ( $p = 0.001$ )<sup>[42]</sup>. In a second study by the same team that evaluated 145 patients with AF, preserved ejection fraction and lateral E/e' ratio <9 at rest, lateral E/e' >9 at exercise was independently associated with a decrease in peak VO<sub>2</sub> ( $p = 0.001$ ), after adjusting for age ( $p = 0.001$ ) and female sex ( $p = 0.001$ )<sup>[43]</sup>. All these findings are consistent with those observed in patients in sinus rhythm<sup>[7,36]</sup>.

Last, E/e' offers useful prognostic information in patients with AF and heart failure with preserved ejection fraction. In one study that specifically included 148 patients with these 2 conditions, septal E/e' >15 was a good predictor of cardiovascular death, recurrence of heart failure and stroke, with a sensitivity and specificity of 50% and 78%, respectively (area under the ROC curve of 0.65,  $p < 0.01$ )<sup>[44]</sup>.

### Relevance of E/e' in risk stratification in patients with AF

E/e' used as a noninvasive surrogate for left ventricular diastolic pressures provides important prognostic information in multiple populations of patients in sinus rhythm<sup>[4-6,9,10,12,13,16,17,19-21,24]</sup>. AF is linked to outcome, and several studies have specifically addressed the clinical relevance of E/e' in risk stratification in this clinical setting.

Three studies first reported the relevance of E/e' in predicting death in patients with AF. In the landmark study by Okura et al., 230 patients with AF were followed, and septal E/e' >15 was an independent predictor of mortality ( $p = 0.03$ ), after adjusting for age ( $p = 0.02$ )<sup>[45]</sup>. In another recent work that included 488 patients with AF and preserved ejection fraction, septal E/e' >15 was independently associated with mortality ( $p < 0.01$ ), after adjusting for hemoglobin ( $p < 0.001$ )<sup>[46]</sup>. In a prospective, multicenter study that observed 971 patients with AF, average E/e' >13 was an independent predictor of death ( $p = 0.03$ )<sup>[47]</sup>.

This noninvasive index is also a potent risk marker of left atrial appendage thrombus in patients with AF<sup>[48-50]</sup>. In a first study that evaluated 376 consecutive patients with AF, septal E/e' >13 was a predictor of left atrial appendage thrombus in multivariate analysis ( $p = 0.02$ ), after adjusting for left ventricular ejection fraction ( $p = 0.005$ ) and left atrial size ( $p = 0.04$ )<sup>[48]</sup>. In another recent study that included 563 consecutive patients with AF, septal E/e' >12 and lateral E/e' >9.4 predicted left atrial appendage thrombus in multivariate analysis ( $p < 0.01$ ), with a sensitivity in thrombus detection close to 100% for a specificity between 38 and 55%<sup>[50]</sup>. In the landmark study of Lee et al. that evaluated 330 patients with AF and preserved ejection fraction, septal E/e' was an independent predictor of stroke in multivariate analysis ( $p < 0.01$ ), with arterial hypertension ( $p < 0.01$ )<sup>[51]</sup>. In another study that observed 1098 consecutive patients with paroxysmal AF, septal E/e' >15 was a powerful, independent predictor of stroke ( $p = 0.03$ )<sup>[52]</sup>. Last, in a recent observational study that included 171 neurologically asymptomatic patients with AF, septal E/e' >12.4 was independently associated with silent cerebral infarction at MRI ( $p = 0.001$ ), after adjusting for age ( $p = 0.025$ )<sup>[53]</sup>. The clinical relevance of E/e' has also been reported in the prediction of cardiovascular events in patients with AF. In the observational study by Su et al, 196 patients

with AF were followed for 17 months<sup>[54]</sup>. Average E/e' independently predicted death and hospitalization for heart failure ( $p=0.002$ ), after adjusting for a history of chronic heart failure ( $<0.001$ ), left ventricular mass index ( $p=0.001$ ) and mitral L wave ( $p=0.016$ ). In another study that observed 190 patients with AF, increased average E/e' was related to death and hospitalization for heart failure in univariate analysis ( $p<0.001$ )<sup>[55]</sup>. In another observational study that prospectively followed 196 consecutive patients with AF for about 17 months, an abnormal value for average E/e' was associated with sudden death, stroke and hospitalization for heart failure ( $p=0.001$ ), after adjusting for chronic heart failure ( $p=0.002$ ) and the myocardial performance index ( $p=0.004$ )<sup>[56]</sup>. Similar results have been reported in another observational study that followed 252 consecutive patients with AF for 21 months<sup>[57]</sup>. Average E/e'  $>8$  was a powerful predictor of the composite end-point of cardiovascular death, progression of heart failure and stroke ( $p<0.001$ ), after adjusting for left atrial volume and left atrial deformation by twodimensional speckle tracking echocardiography. Last, there is convincing evidence that E/e' predicts left atrial appendage thrombus, neurological events and, more generally, cardiovascular events beyond the CHA<sub>2</sub>DS<sub>2</sub>-VASC score<sup>[47,49,53,57,58]</sup>.

### Relevance of E/e' in Predicting Recurrence of AF after Catheter Ablation or Cardioversion

The relevance of invasive left atrial pressure recording in predicting recurrence of AF after catheter ablation has recently been reported by invasive means in patients referred for catheter ablation, which may be in part related to its contribution to left atrial stretch and remodeling<sup>[59,60]</sup>. In one study that included 170 patients referred for ablation procedure, invasive left atrial pressure was a powerful predictor of recurrence of arrhythmia in multivariate analysis ( $p=0.006$ ), after adjusting for left atrial volume ( $p=0.007$ )<sup>[60]</sup>. Noninvasive assessment of left ventricular diastolic pressures may therefore be useful in predicting recurrence of arrhythmia in daily practice. Several studies have addressed the relevance of E/e' in the prediction of arrhythmia recurrence after catheter ablation and electrical cardioversion. In the study by Li et al., 103 consecutive patients were included<sup>[61]</sup>. E/e' measured during AF and after sinus rhythm restoration was a powerful predictor of recurrence of AF after ablation in multivariate analysis ( $p<0.001$ ). Septal E/e'  $>11.2$  measured before ablation had a sensitivity and specificity of 81 and 82%, respectively, in the prediction of recurrence of arrhythmia. These results were confirmed in 198 patients with paroxysmal AF<sup>[62]</sup>. Average E/e'  $>13$  was the sole Doppler echocardiographic parameter associated with recurrence of arrhythmia. Okamoto et al. evaluated the usefulness of E/e' in 22 patients with AF and hypertrophic cardiomyopathy<sup>[63]</sup>. Septal E/e'  $>15$  independently predicted recurrence of arrhythmia after catheter ablation ( $p=0.03$ ). Last, the most recent study that included 215 consecutive patients with AF referred for catheter ablation has offered confirmatory findings. Average E/e'  $>14$  was a powerful, independent predictor of arrhythmia recurrence after multiple ablation procedures ( $p=0.02$ ), after adjusting for age, sex, lowvoltage-area existence and left atrial diameter<sup>[64]</sup>.

In one study by Caputo et al., lateral E/e' was independently associated with recurrence of AF in 51 patients referred for electrical cardioversion ( $p=0.0078$ ), after adjusting for left atrial volume ( $p$

$=0.04$ )<sup>[65]</sup>. Confirmatory results were observed in patients with or without left atrial dilatation. In one study that included 127 patients with left atrial dilatation, septal E/e'  $>11$  predicted recurrence of AF after cardioversion ( $p=0.001$ ) in multivariate analysis, after adjusting for duration of arrhythmia before cardioversion ( $p=0.04$ ) and systolic pulmonary arterial pressure ( $p=0.001$ )<sup>[66]</sup>. In another study that included 66 patients with AF and left atrial diameter  $<50$  mm, septal E/e' was independently associated with recurrence of arrhythmia after cardioversion ( $p=0.017$ ), after adjusting for left atrial volume ( $p=0.04$ )<sup>[67]</sup>.

### Conclusion

E/e' is a user-friendly and reliable Doppler index in semi-quantitative assessment of left ventricular diastolic pressures in patients with AF. However, at this time, several consecutive cycles must be recorded and averaged in the absence of simultaneous measurement of E and e' velocities to overcome potential influence of cycle irregularity on E and e' values. Evidence of an abnormal value for E/e' at rest and during exercise strengthens the diagnosis of heart failure with preserved ejection fraction and provides prognostic information on outcome and arrhythmia recurrence. In light of these findings, the measure of E/e' should be an integral part of the evaluation of any patient with AF referred for comprehensive transthoracic Doppler echocardiography. It should be kept in mind that the adoption of a higher threshold value for the E/e' ratio improves the positive predictive value of disease or event but, at the same time, impairs the negative predictive value. In addition, Measuring e' velocity by color tissue Doppler imaging might be an alternative in this setting despite paucity of data on the diagnostic and prognostic relevance of this method and the constant overestimation of spectral E/e' by color E/e'<sup>[68-72]</sup>. Accordingly, further experimental and clinical studies are mandatory to delineate the potential contribution of each method to measure E/e' according to all the aspects of cardiovascular diseases.

### Conflicts of Interest

None

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