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Average e′ velocity on transthoracic echocardiogram is a novel predictor of left atrial appendage sludge or thrombus in patients with atrial fibrillation

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Background: Studies have demonstrated the value of transthoracic echocardiogram (TTE) diastolic parameters in predicting left atrial appendage (LAA) thrombus; however, these studies have been small. We aim to clarify the relationship between TTE diastolic parameters, in particular average e′, and LAA thrombus or sludge.

Methods: A case-control review was conducted of subjects with non-valvular atrial fibrillation (n = 2263) who had undergone TEE (transesophageal echocardiogram) and had a TTE within 1 year of TEE. Cases of LAA sludge or thrombus were matched to controls by age, sex, left ventricular ejection fraction (LVEF), and anticoagulation status.

Results: Forty-three subjects (mean age 73 ± 12, 65% male, LVEF 47%, 44% on anticoagulation) with LAA sludge or thrombus were identified. Compared to matched controls, average TTE e′ (7.3 ± 2.1 cm/s vs 8.7 ± 2.1 cm/s, $P < 0.001$) and the E:e′ ratio (15 ± 7 cm/s vs 12 ± 5 cm/s; $P = 0.005$) were significant predictors of LAA sludge or thrombus. Average TTE e′ value of >11 cm/s had 100% sensitivity for ruling out LAA sludge or thrombus.

Conclusion: In individuals with atrial fibrillation, average e′ >11 cm/s on TTE is a promising independent predictor of the absence of LAA sludge or thrombus on TEE.

KEYWORDS
arrhythmias, diagnostic Testing, echocardiography, embolism, left atrial appendage thrombus

1 | INTRODUCTION

As many as 15% of patients presenting with atrial fibrillation of more than 48 hours or unknown duration will have a left atrial appendage (LAA) thrombus.[1] These thrombi are a consequence of the poor contractile state in the LAA which leads to stasis.[2,3] Traditionally transesophageal echocardiogram (TEE) is used to directly visualize the LAA for thrombus formation.[4] Potential disadvantages of TEE include the invasiveness, cost, rare but serious complications, and the need for a cardiologist qualified to perform and interpret the study.[5] In an effort to develop non-invasive prediction models to rule out a LAA thrombus, it has been hypothesized that impaired diastolic function potentiates venous stasis within the LAA.[6,7] Previous studies including small numbers of subjects have shown that markers of diastolic dysfunction on transthoracic echocardiogram (TTE) are all independent predictors of LAA thrombus formation.[8,9] One set of diastolic markers, the e′ velocity holds particular promise in its use in a prediction model. The medial and lateral e′ velocities measure the longitudinal expansion of the mitral valve annulus during diastole, with the lateral e′ velocity having a close anatomic relationship to the LAA.[6,10] Furthermore unlike other diastolic parameters diagnosed on TTE, the e′ velocity is relatively independent of hemodynamic changes.[10] Previous studies examining the predictive value of e′ velocity have shown an association with LAA thrombus formation.[8,9] These studies have been small and more evidence and validation of these findings are needed in a larger cohort of subjects prior to their implementation. The purpose of our study is to further clarify the relationship between TTE diastolic parameters and in particular the e′ velocity and the absence of LAA thrombus or sludge.

2 | METHODS

A case-control study was performed by accessing and merging the echocardiogram database of NYU Langone Medical Center with corresponding clinical data from the electronic health record between January 1st 2010 and December 31st 2015. All adult subjects who had undergone a TEE and carried a diagnosis of a non-valvular atrial tachyarrhythmia (permanent, paroxysmal or chronic atrial fibrillation, atrial flutter, and atrial tachycardia) were identified. Cases were defined as those subjects who at the time of TEE were diagnosed with a LAA thrombus or sludge. Controls were randomly selected after the initial search and matched to cases based on: Age range at time of TEE (80 or greater, 79–70, 69–60, 59–50, 49 or less), sex, left ventricular ejection fraction (LVEF) at time of TTE (50% or greater, 49–41, 40–31, 30% or less, classifications as outlined in the AHA/ACC guidelines[11]), and anticoagulation status (none or 21 days or less, or greater than 21 days).[5] Selection of controls to match to cases was blinded with regards to TTE diastolic parameters. This study was approved by the New York University Institutional Review Board, due to the retrospective nature of the study, no informed consent was required.

Cases and controls were selected for analysis if a TTE was performed within 1 year of the TEE or at the time of the index event which required a TEE and there was no change in LVEF, no acute coronary events (defined as chart documentation of a hospitalization for an acute coronary syndrome) or any electrophysiology procedure between the time of TEE and TTE. Cases and controls were excluded for any reason that would make e′ or the E:e′ ratio inaccurate. These included severe mitral regurgitation, greater than moderate mitral annular calcification, or a mitral valve replacement or repair procedure.[10] Additional exclusion criteria included missing lateral e′ recording or inability to determine anticoagulation status, as well as anticoagulation compliance through the use of medical records and chart review.

For the main outcome variable (LAA thrombus or sludge), a thrombus was defined as a circumscribed intracavitary echodense mass which could be visualized in multiple views and distinct from the left atrium or LAA and pectinate muscles. Sludge was defined as having precipitous spontaneous echocontrast without a discernible mass.[12] Equivocal cases that could not be determined through echocardiogram database review were visually reviewed offline by a blinded National Board of Echocardiography (NBE) certified physician. The main predictor variables (lateral and medial e′ velocity) were all obtained by an NBE certified echocardiographer. Measurements were performed by placing the pulse wave tissue Doppler signal at the lateral and medial mitral valve annulus, respectively, taken in early diastole and averaged over 3–5 beats. Average e′ was calculated as the lateral plus medial e′ recording divided by 2.[13] In order to limit potential measurement errors of our main predictor variable e′, all e′ measurements from the original echocardiogram recordings were measured offline by a blinded NBE certified physician (Figure 1). When atrial fibrillation was noted, an average of 5–10 heartbeats was used to calculate the e′ velocities.

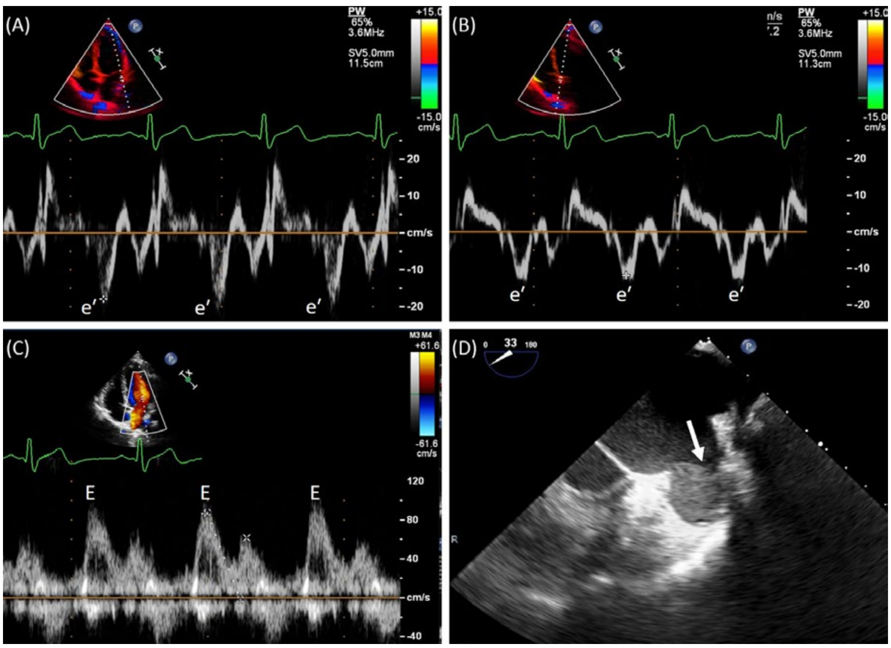

FIGURE 1 Representative images highlighting transthoracic and transesophageal echocardiogram measurements. Tissue Doppler recording lateral (A) and medial (B) e′ measurements. Pulsed-wave Doppler recording of mitral inflow velocity (C). Left atrial appendage thrombus (D - arrow)

The additional TTE measurements such as interventricular and posterior left ventricular wall thickness, left ventricular internal end diastolic and end systolic diameter measurements, valvular regurgitation and stenosis as well as E and a velocities were obtained through New York University echocardiogram database review which are routinely measured and recorded by NBE certified echocardiographers using standard American Society of Echocardiography guidelines.[14] E (during early diastole) and a-wave velocities (late diastole, when subjects were in normal sinus rhythm) were obtained using pulse wave velocity with the sample volume placed between the mitral valve leaflet tips. Left ventricular mass was calculated through use of the Devereux formula and indexed to body surface area.[14] LVEF was measured with the Simpson's biplane method.[14] Left atrial volume index was measured by the biplane area-length method and indexed to body surface area.[14] E:e′ ratio was calculated as the mitral valve maximum E velocity divided by the average e′ velocity. When medial e′ was missing, the E: lateral e′ was used.[13]

Medical history, medications, creatinine, and hemoglobin A1c were obtained for all cases and controls through chart review and ICD-10 coding. Components of the CHA_2DS_2-VAS_c were collected including: systolic heart failure (LVEF ≤ 40), diabetes mellitus type II (chart documentation, prescribed diabetic medication, hemoglobin A1c ≥6.5, or ICD-10 code), stroke or transient ischemic attack (chart documentation, ICD-10 code), hypertension (chart documentation, ICD-10 code, prescribed anti-hypertensive medications), and vascular disease (including chart documented peripheral vascular disease, coronary artery disease, ICD-10 code, catheterization films or reports, and history of a positive stress test) were obtained. Heart failure with preserved ejection fraction was defined through chart review and ICD-10 coding.

Baseline differences in the subjects as compared with their matched controls were assessed through stratified linear regression for continuous variables and conditional logistic regression for categorical ones. Conditional logistic regression analysis was used to assess the association between E:e′ ratio, e′ velocity, and LAA thrombus. Multivariate regression models were constructed in a stepwise approach to account for potential echocardiographic and clinical covariates and confounders (left atrial volume index, left ventricular mass index, diabetes mellitus type II, vascular disease, and history of transient ischemic attack or stroke). Diastolic TTE variables directly related to one another (E:e′ ratio, medial, lateral, and average e′) were not placed into the same logistic regression model due to inherent co-linearity. To enhance clinical applicability, receiver operator curve characteristics (ROC) were created for single diastolic predictor variables and areas under the curve calculated. A corresponding cutoff for each prognostic predictor was defined as using the largest cutoff value such that sensitivity equaled 1. SPSS (IBM Corp, v.20, Armonk, NY) was used for creation of the receiver operator curves and, STATA (v. 11, College Station, TX 2009) for the remaining data analysis. Based on a previous study showing a greater than 25% difference in lateral e′ velocity between those with and without LAA thrombus, we calculated that using a 1–3 case to control ratio with at least 40 cases and 120 controls we would have a 90% power to detect a 20% difference in e′ velocity with an alpha level of 0.05.[8] A two-tailed *P*-value less than 0.05 was considered significant.

3 | RESULTS

Initial search of the echocardiography database yielded a total of 10,012 TEEs of which 5,568 had TTEs performed at NYU within 1 year of the corresponding TEE. Of these corresponding matched TTEs to TEEs, 2263 had a medical history of an atrial tachyarrhythmia (atrial tachycardia, atrial fibrillation, or atrial flutter). Within this cohort, there were a total of 91 (4%) subjects with either thrombi or sludge identified of which 43 met inclusion criteria. Of the 43 included cases, 27 had only thrombus, 13 had sludge and thrombus and 3 had sludge only.

A total of 129 controls matched to their corresponding cases were chosen from the remaining subjects identified in the echocardiographic atrial tachyarrhythmia database. In the total combined case-control cohort, the indication for TEE included direct current cardioversion in 84 (48%) subjects, atrial fibrillation or atrial tachycardia ablation in 64 (37%) subjects, evaluation for a LAA closure device in 8 (5%) and 9 (10%) for other reasons. At the time of TEE, 128 (75%) were in atrial fibrillation, 6 (3%) were in atrial flutter, 6 (3%) were in an atrial tachycardia, 22 (13%) were in sinus rhythm, and 10 (6%) were paced. The majority of the subjects were Caucasian, 147 (85%) and Hispanic 13 (8%). Seven (4%) were African American, and 5 (3%) were Asian.

The baseline characteristics of cases compared with controls are listed in Table 1. Based on pre-determined matching, cases and controls were equally matched for age, sex, heart failure with reduced ejection fraction, and anticoagulation status at the time of TEE and similar with respect to hypertension, coronary artery disease, peripheral vascular disease, and total CHA_2DS_2-VAS_c score (Table 1). The average EF for the entire cohort was 49 ± 17%. Thirty percent (n = 13) of the cases and 29% (n = 37) of the controls had an EF ≤ 35% (*P* = 0.85). By study design, all cases and controls on a novel oral anticoagulant had documented chart medication compliance for >3 weeks. The mean INR for cases and controls of those on Coumadin for >3 weeks at the time of TEE is listed in Table 1. Despite documented compliance with Coumadin for >3 weeks, 30% of controls and 40% of cases had an INR less than 2.0 at the time of TEE. Cases compared with matched controls were more likely to have heart failure with preserved ejection fraction and trended towards more cases of diabetes mellitus type II and transient ischemic attack or stroke. Approximately one quarter of the total cohort had undergone previous cardioversion and required previous antiarrhythmic therapy. Both groups had an equal number of pacemaker and implantable cardioverter defibrillator implantations (Table 1).

The median time from TTE to TEE was 1 day (IQR in days 136) for controls and 1 day for cases (IQR in days 1–3, *P* = 0.24). Average LVEF and left ventricular end diastolic diameter were similar across both groups (Table 2). Mean E:e′ ratio was significantly higher among cases of LAA thrombus or sludge compared to controls. Medial,

TABLE 1 Baseline characteristics

	Left atrial appendage evaluation		
	Thrombus/sludge absent (n = 129)	**Thrombus/sludge present (n = 43)**	***P* - value**
Age (y), mean ± SD	73 ± 12	73 ± 12	0.96
BMI (kg/m^2), mean ± SD	29 ± 7	30 ± 7	0.92
Male sex, n (%)	84 (65%)	28 (65%)	1.00
Hypertension, n (%)	95 (73%)	30 (69%)	0.61
ACE-I/ARB, n (%)	62 (48%)	28 (65%)	0.06
Diabetes mellitus type II, n (%)	29 (21%)	15 (35%)	0.07
Systolic heart failure, n (%)	45 (35%)	16 (37%)	0.78
HFpEF, n (%)	19 (15%)	12 (28%)	0.04
Coronary artery disease, n (%)	44 (34%)	15 (37%)	0.77
Peripheral vascular disease, n (%)	7 (5%)	3 (7%)	0.71
Stroke or TIA, n (%)	11 (9%)	7 (16%)	0.15
CHA_2DS_2-VAS_c, mean ± SD	3.3 ± 1.5	3.6 ± 1.6	0.36
Aspirin, n (%)	55 (42%)	25 (59%)	0.04
Thienopyridine, n (%)	15 (12%)	5 (12%)	1.00
Therapeutic anticoagulation, n (%)[a]	57 (44%)	19 (44%)	1.00
Coumadin, n (%)	28 (22%)	11 (26%)	0.48
Novel oral anticoagulant, n (%)[b]	29 (22%)	8 (19%)	0.49
Days from TTE to TEE, median [IQR]	1 [1–3]	1 [1–36]	0.24
Electrophysiology characteristics			
AF at time of TEE, n (%)	93 (72%)	35 (81%)	0.51
Previous ablation, n (%)	24 (19%)	3 (8%)	0.12
Previous cardioversion, n (%)	29 (22%)	8 (21%)	0.81
Current antiarrhythmic use, n (%)	32 (25%)	8 (19%)	0.34
Pacemaker, n (%)	14 (11%	7 (16%)	0.33
ICD, n (%)	10 (8%)	5 (12%)	0.42
Laboratory values			
Creatinine (mg/dL), mean ± SD	1.2 ± 1.2	1.3 ± 1.4	0.57
Hemoglobin A1c	6.1 ± 0.8	6.7 ± 1.7	0.02
INR[c]	2.3 ± 0.6	1.97 ± 0.6	0.10

ACE-I/ARB = angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VAS_c = age, sex, heart failure, hypertension, diabetes, stroke or transient ischemic attack, vascular disease; ICD = implantable cardioverter defibrillator; HFpEF = heart failure with preserved ejection fraction > 40% with chart documentation of heart failure symptoms; Systolic Heart Failure, left ventricular ejection fraction ≤40%; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram; IQR = interquartile range; TIA = transient ischemic attack.
[a]Therapeutic anticoagulation is documented compliance with oral anticoagulants >3 wk.
[b]Novel oral anticoagulant = dabigatran, apixaban, rivaroxaban.
[c]INR was taken from those on Coumadin for >3 wk at the time of TEE.

lateral, and average e′ were all significantly lower among cases compared with controls (Table 2). Left atrial volume index was higher, and a trend was noted of a higher Left ventricular mass index in cases compared to controls (Table 2). For TEE measured variables, in cases compared with controls there were more cases of LAA smoke and a lower LAA emptying velocity. In sensitivity analysis stratifying e′ velocities by those on and off anticoagulation as well as those with a TTE to TEE duration of 5 days or less, a statistical difference still remained between cases and controls across E:e′ ratio and all e′ diastolic parameters.

Table 3 shows prediction models accounting for various covariates and confounders to determine the association between diastolic TTE measurements and LAA sludge or thrombus at the time of TEE. A higher E:e′ ratio, and lower medial e′, lateral e′, and average e′ were all associated with LAA sludge or thrombi (model 1, Table 3). With the addition of TTE parameters (left atrial volume index and left ventricular mass index) and remaining CHA_2DS_2-VAS_c variables not included in initial matching criteria these associations remained significant (model 2 and model 3, Table 3). In the final model, the medial e′ and average e′ revealed the strongest predictors of LAA sludge or thrombus. A 1 cm/s rise in medial e′ or average e′ yielded an odds ratio of 0.64 and 0.66, respectively, for diagnosis of LAA thrombus or sludge at the time of TEE (Table 3). Exclusion of LAA sludge from the analysis (3 cases of sludge, 9 matched controls) yielded similar odds ratios and *P* – values for models 1, 2, and 3. Sensitivity analysis revealed no change in the odds ratios for models 1, 2, and 3 across all diastolic predictors when stratified by anticoagulation status at the time of TEE.

Of the TTE parameters, medial e′ and the average e′ velocities had the strongest ROC discriminatory capacity for LAA sludge or thrombi with an area under the curve of 0.713 and 0.705, respectively ($P < 0.001$) (Figure 2; Table 4). E:e′ and lateral e′ were less predictive with an area under the curve of 0.658 and 0.635, respectively. When obtaining an average e′ velocity of greater than 11 cm/s on TTE, there was 100% sensitivity for ruling out LAA sludge or thrombi on TEE (Table 4). Of the 12 subjects with an average e′ >11 cm/s (Table 4), 75% (n = 9) had a CHA_2DS_2-VAS_c greater than 1. Analysis of E:e′ ratio, medial, lateral, and average e′ showed nonsignificant differences in the ROC discriminatory capacity between these diastolic predictors. Of the TEE parameters, the ROC discriminatory capacity was the strongest for LAA emptying velocity with an area under the curve of 0.861, $P < 0.001$ (Figure 2).

4 | DISCUSSION

In this matched case-control study for age, sex, LVEF, and anticoagulation status, e′ velocities on TTE were independently associated with LAA thrombus or sludge on TEE (Table 3). To further validate

TABLE 2 Echocardiographic characteristics

	Left atrial appendage evaluation		
	Thrombus/sludge absent (n = 129)	Thrombus/sludge present (n = 43)	*P* - value
Transesophageal echocardiogram			
LAA emptying velocity (cm/s), mean ± SD[a]	44 ± 19	23 ± 14	<0.001
LAA Smoke	30 (23%)	35 (81%)	<0.001
Transthoracic echocardiogram			
LVEF (%), mean ± SD	50 ± 17	47 ± 17	0.30
E:e′ ratio, mean ± SD	12 ± 5	15 ± 7	0.005
Medial e′ (cm/s), mean ± SD[b]	7.2 ± 2.1	5.7 ± 1.7	<0.001
Lateral e′ (cm/s), mean ± SD	10.2 ± 2.8	8.7 ± 2.6	0.001
Average e′ (cm/s), mean ± SD[b]	8.7 ± 2.1	7.3 ± 2.1	<0.001
LA volume index (mL/m^2), mean ± SD	35 ± 12	44 ± 16	0.001
LVEDD (cm), mean ± SD	4.8 ± 0.9	4.8 ± 0.9	0.90
LV mass Index (g/m^2), mean ± SD	100 ± 31	110 ± 32	0.07

LA = left atrial; LAA = left atrial appendage; LVEDD = left ventricular end diastolic diameter; LV = left ventricular; LVEF = left ventricular ejection fraction.
[a]Case n for LAA emptying velocity was 39 due to missing measurements.
[b]Control n for medial e′ and average e′ was 123 due to missing e′ measurements.

TABLE 3 Model to predict left atrial appendage thrombus or sludge

	Model 1			Model 2			Model 3		
Diastolic predictor	OR	95% CI	Sig	OR	95% CI	Sig	OR	95% CI	Sig
E:e′ ratio	1.11	1.03–1.18	0.004	1.08	1.01–1.16	0.023	1.08	1.01–1.16	0.022
Medial e′ (cm/s)	0.64	0.51–0.81	<0.001	0.65	0.50–0.85	0.001	0.64	0.49–0.84	0.001
Lateral e′ (cm/s)	0.83	0.72–0.94	0.005	0.80	0.69–0.93	0.004	0.82	0.69–0.93	0.004
Average e′ (cm/s)	0.69	0.56–0.84	<0.001	0.67	0.53–0.84	0.001	0.66	0.52–0.83	0.001

95% CI = 95% confidence interval; OR = odds ratio; Sig = *P* – value. Model 1; Univariate association between diastolic predictor and left atrial appendage thrombus or sludge. Model 2; Multivariate association accounting for left atrial volume index and left ventricular mass index between other diastolic predictors and left atrial appendage thrombus or sludge. Model 3; Model 2 plus the remaining CHA_2DS_2-VAS_c variables not accounted for in matching (diabetes, vascular disease, hx of stroke, or transient ischemic attack).

the potential of the e′ values to rule out sludge or thrombus, multivariate analysis using transthoracic (Table 3, model 2) and clinical covariates and confounders (Table 3, model 3) continued to show an association between e′ and LAA sludge or thrombus.

In this study, controls were matched to cases in order to create a similar CHA_2DS_2-VAS_c score between the two groups (Table 1) as well as what we felt to be the strongest determinant of LAA sludge or thrombus, active anticoagulation at the time of TEE. As expected, due to matching, the ROC revealed no discriminatory capacity for CHA_2DS_2-VAS_c score to predict the outcome (area under the curve 0.53, $P = 0.6$). Table 4, Figure 2 suggests absolute cutoff values for 100% sensitivity in ruling out LAA sludge or thrombus at the time of TEE based on the ROC discriminatory capacity of the e′ variables. As the consequences of a missed LAA thrombus may result in stroke, the sensitivity of any potential TTE predictor must be near 100%. Using a cutoff of lateral e′ velocity greater than 13 cm/s, medial e′ greater than 10 cm/s or average e′ greater than 11 cm/s one could predict with 100% sensitivity in our database that 16, 10, and 12 subjects, respectively, would not have a LAA sludge or thrombus at the time of TEE. Due to matching in our study these e′ values are able to be applied clinically regardless of age, sex, LVEF, or anticoagulation status at the time of TEE.

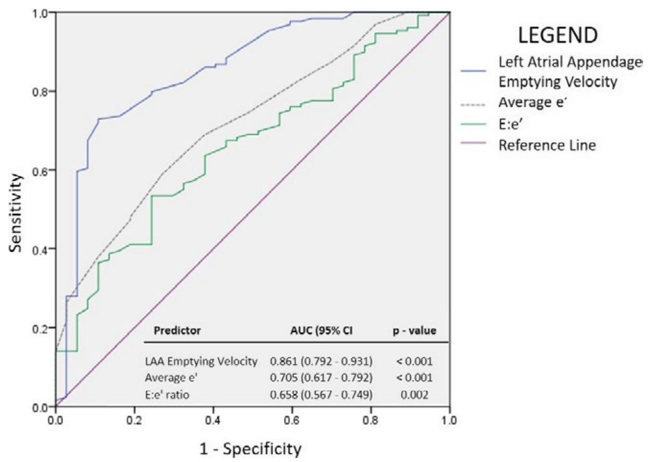

FIGURE 2 Receiver operator curve discriminatory capacity for univariate predictors of left atrial appendage sludge or thrombus. The *P*-values in this figure are as compared to the C statistic with random guess (0.5). The AUC difference between LAA emptying velocity and average e′ ($P = 0.003$) and LAA emptying velocity and E:e′ ratio ($P < 0.001$) were significant. No difference between E:e′ ratio and average e′ ($P = 0.25$) was noted. AUC (95% CI); Area under the curve, 95% confidence interval. LAA: left atrial appendage

The biological plausibility of our findings that e′ is related to LAA thrombus formation is based on previous work suggesting a relationship between the LAA flow, left ventricular relaxation and e′ as a measure of diastolic dysfunction.[6] It has been hypothesized that ventricular expansion during diastole contributes to LAA emptying through the pericardial compression of the LAA appendage during early diastolic filling which would therefore explain reduced LAA emptying in those with diastolic dysfunction.[15] The low LAA filling patterns within the LAA appendage leads to venous stasis thus precipitating thrombus formation.[16]

Other studies of diastolic parameters have shown results consistent with ours. A 2006 analysis of 3700 subjects undergoing a TEE with a diagnosis of atrial fibrillation revealed a 5% incidence of LAA thrombus with a significant association noted for left atrial volume index.[17] More recent data have shown associations with left ventricular mass and left ventricular volume index.[7] The e′ velocity has also recently shown associations with LAA thrombus formation. A 2014 retrospective cohort series of subjects with atrial fibrillation undergoing a TEE analyzed 19 cases of thrombi with 297 controls. The authors found that E:e′ ratio and lateral e′ were the strongest predictors of LAA thrombus after adjustment for anticoagulation status and the CHA_2DS_2-VAS_c score. These findings were recently confirmed by the same authors in a prospective series with 17 cases of thrombus showing strong ROC discriminatory capacity

TABLE 4 Receiver operator curve characteristics

Predictor	Cutoff value to rule out LAA thrombus or sludge[a]	Controls above cutoff value, n (%)[b] n = 129[c]	AUC (95% CI)	*P*-value[*]
CHA_2DS_2-VAS_c score	–	–	0.530 (0.430–0.620)	0.604
LAA emptying velocity	–	–	0.861 (0.792–0.931)	<0.001
E:e′ ratio	<7	14 (11%)	0.658 (0.567–0.749)	0.002
Medial e′	>10 cm/s	10 (8%)	0.713 (0.623–0.804)	<0.001
Lateral e′	>13 cm/s	16 (12%)	0.635 (0.542–0.728)	0.008
Average e′	>11 cm/s	12 (10%)	0.705 (0.617–0.792)	<0.001

AUC = area under the curve; CHA_2DS_2-VAS_c = age, sex, heart failure, hypertension, diabetes, stroke, or transient ischemic attack, vascular disease; LAA = left atrial appendage.

[a]The cutoff value is defined as the diastolic predictor cutoff value to achieve 100% sensitivity to rule out a LAA thrombus or sludge at the time of transesophageal echocardiogram.

[b]Controls above the cutoff value is defined as the amount of controls in our study that meet the 100% diastolic predictor sensitivity criteria for ruling out thrombus or sludge.

[c]Control n for medial e′ and average e′ was 123 due to missing medial e′ measurements.

[*]*P*-value is the comparison of the C statistic with random guess (0.5).

of both E:e′ ratio and e′ to exclude LAA thrombus independent of CHA_2DS_2-VAS_c.[18]

Our study is unique in several regards. This analysis with 43 sludge or thrombi is the largest to analyze and demonstrate an association between e′ and LAA thrombus. The case-control design allowed for an evenly matched CHA_2DS_2-VAS_c score among cases and controls as well as matched anticoagulation status at the time of TEE potentially eliminating the strongest confounders. Our study introduces a dichotomous variable, average e′ >11 cm/s, as a clinically useful predictor of the absence of LAA thrombus. Finally, studying this association in a different patient population than previously studied allows for increased external validity.

Limitations to our study include the retrospective nature thereby potentially allowing for bias in selection of controls. We attempted to eliminate this bias through matching to age, sex, and LVEF. Clinically when using e′ in a prediction model to rule out LAA sludge or thrombus, there could be measurement variability due to placement of the Doppler signal or interpretation of the e′ value when patients are in atrial fibrillation. We attempted to limit this measurement variability through the examination of the average e′ to predict LAA sludge or thrombus. Additionally, the temporal relationship between the TTE and TEE in our study for some of the subjects may have been poor. We attempted to correct for this bias by validating the e′ velocity which changes less over time and is not sensitive to preload conditions. We also performed a sensitivity analysis just assessing those with TTEs less than 5 days prior to the TEE which showed no change to the outcome variables. A ROC analysis and specificity calculations is based on the sample population studied, thus our sample size and case-control study design place some limitations on our ability to validate the scoring system as well as calculate a specificity. When calculating the ROC discriminatory capacity, the clinical need to achieve 100% sensitivity of our predictor variables could potentially lead to a low applicability. However, diastolic parameters are routinely obtained on TTE and even 1 fewer TEE needing to be performed is clinically meaningful.

In conclusion, we found that in a large case-control study that the e′ velocity and the E:e′ ratio on TTE were highly predictive of LAA sludge or thrombus on TEE. This association was independent of anticoagulation status, CHA_2DS_2-VAS_c score as well as left atrial and left ventricular size. An average e′ velocity of greater than 11 cm/s had 100% sensitivity for absence of LAA thrombus or sludge. This study confirms that diastolic dysfunction contributes to LAA dysfunction and provides further evidence that diastolic parameters can be used as a method to predict or rule out a LAA thrombus. If confirmed in larger prospective studies, average e′ velocity of greater than 11 cm/s may represent a novel independent predictor of the absence of LAA thrombus. This would be useful clinically in deciding the best approach to anticoagulation and need for TEE prior to cardioversion. We recommend continued retrospective and prospective analysis with an aim of including average e′ velocity on TTE of greater than 11 cm/s as an easily obtained independent predictor in clinical atrial fibrillation management guidelines.

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REFERENCES

1. Manning WJ, Silverman DI, Keighley CS, Oettgen P, Douglas PS. Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5-year study. *J Am Coll Cardiol*. 1995;25(6):1354–1361.
2. Fatkin D, Kelly R, Feneley MP. Left atrial appendage blood velocity and thromboembolic risk in patients with atrial fibrillation. *J Am Coll Cardiol*. 1994;24(5):1429–1430.
3. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol*. 1994;23(4):961–969.
4. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344(19):1411–1420.
5. Klein AL, Murray RD, Grimm RA. Role of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation. *J Am Coll Cardiol*. 2001;37(3):691–704.
6. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart*. 1999;82(5):547–554.
7. Ayirala S, Kumar S, O'Sullivan DM, Silverman DI. Echocardiographic predictors of left atrial appendage thrombus formation. *J Am Soc Echocardiogr*. 2011;24(5):499–505.
8. Doukky R, Garcia-Sayan E, Gage H, et al. The value of diastolic function parameters in the prediction of left atrial appendage thrombus in patients with nonvalvular atrial fibrillation. *Cardiovasc Ultrasound*. 2014;12:10.
9. Gaber R, Salama M. Left atrial appendage dysfunction in acute embolic stroke young patients with sinus rhythm: correlation with Tissue Doppler mitral annular systolic velocity. *Artery Res*. 2016;15:12–18.
10. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321–1360.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147–e239.
12. Hahn RT, Abraham T, Adams MS, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *Anesth Analg*. 2014;118(1):21–68.
13. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277–314.

14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1–39. e14.
15. Akosah KO, Funai JT, Porter TR, Jesse RL, Mohanty PK. Left atrial appendage contractile function in atrial fibrillation. Influence of heart rate and cardioversion to sinus rhythm. *Chest*. 1995;107(3):690–696.
16. Verhorst PM, Kamp O, Visser CA, Verheugt FW. Left atrial appendage flow velocity assessment using transesophageal echocardiography in nonrheumatic atrial fibrillation and systemic embolism. *Am J Cardiol*. 1993;71(2):192–196.
17. Ellis K, Ziada KM, Vivekananthan D, et al. Transthoracic echocardiographic predictors of left atrial appendage thrombus. *Am J Cardiol*. 2006;97(3):421–425.
18. Doukky R, Garcia-Sayan E, Patel M, et al. Impact of diastolic function parameters on the risk for left atrial appendage thrombus in patients with nonvalvular atrial fibrillation: a prospective study. *J Am Soc Echocardiogr*. 2016;29(6):545–553.

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