The a’ velocity by tissue-Doppler echocardiography correlates to invasive mean left atrial pressure in patients with normal ejection fraction

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ABSTRACT

Objectives: To evaluate the correlation of a’ velocity by tissue-Doppler measurements with invasively measured mean left atrial pressure in patients with normal ejection fraction.

Design: In this retrospective study, we evaluated the septal a’, lateral a’ and average a’ velocity by tissue-Doppler echocardiography, in 125 in-hospital patients, 1–12 h before an elective pulmonary vein isolation due to intermittent atrial fibrillation, and compared to invasively measured mean left atrial pressure (LAP) during the invasive procedure. The patients, aged 35–81 years, had to be in sinus rhythm at both examinations, no atrial fibrillation during two procedures, no or mild valve disease and normal ejection fraction (>50%).

Results: Invasively measured mean LAP correlated well to septal a’ (r = −0.435), lateral a’ (r = −0.473) and average a’ velocity (r = −0.491). Normal mean LAP (<12 mmHg) was found in 95 patients and elevated mean LAP (>12 mmHg) in 30 patients. The patients with elevated mean LAP had a lower septal a’ velocity (6.5 ± 2.7 vs 8.6 ± 2.3 cm/s; p < .01), lateral a’ velocity (5.9 ± 2.3 vs 8.6 ± 2.1 cm/s; p < .01) and average a’ velocity (6.2 ± 2.4 vs 8.8 ± 2.1 cm/s; p < .01) compared to patients with normal mean LAP. Septal a’, lateral a’ and average a’ velocity were good predictors of elevated mean LAP with AUC of 0.78, 0.83 and 0.82. Average a’ velocity with cut-off < 7.25 cm/s had a sensitivity of 83% and a specificity of 77% to predict elevated mean LAP.

Conclusion: The a’ velocity is a good indicator of mean LAP and might be considered in the evaluation of left ventricle filling pressure in patients with normal ejection fraction.

Introduction

The ASE/EACVI guidelines for the evaluation of left ventricular diastolic function by echocardiography from 2016, confirmed by two large invasive multicenter studies, have solved many difficulties in the evaluation of diastolic left ventricular (LV) dysfunction and increased LV filling pressure, in patients with decreased ejection fraction and in patients with normal ejection fraction and myocardial disease but not entirely in patients without suspicion of myocardial disease [1–4]. To diagnose patients with heart failure with preserved ejection fraction (HFP EF), still remains a significant clinical issue. The authors in the Euro Filling study called for the value of new diagnostic tools [3]. Studies focused on the late diastolic LV filling phase have shown that a failing left atrium and a dominant diastolic pulmonary vein flow profile were correlated to elevated LV end-diastolic pressure and could predict patients with impaired clinical outcome [5–13, 21, 22, 23, 24]. Recent studies using the easily eligible a’ velocity by tissue-Doppler echocardiography as an estimate for the left atrial contractile status have shown interesting results in predicting significant diastolic dysfunction and an elevated LV filling pressure, in patients with reduced systolic function and furthermore its correlation to the pulmonary vein profile has been clarified, both in patients with normal and reduced ejection fraction [5–7]. However, the a’ velocity has never been tested against invasively measured mean left atrial pressure (LAP).

We aimed to study and evaluate the correlation of a’ velocity by tissue-Doppler measurements and invasively measured mean LAP in a study population with normal ejection fraction. Methods

Population

This retrospective study included 298 consecutive patients, who underwent pulmonary vein isolation (PVI), de novo or redo, due to paroxysmal or persistent atrial fibrillation (AF) during the period from February 2018 to January 2020, at the Department of Heart-Lung-Clinical Physiology, Örebro University Hospital, Sweden. Complete transoesophageal (TEE) and transthoracic (TTE) echocardiography were
accomplished preceding the PVI with 1–12 h. The echo-
doppler examinations were performed by five different
physicians, all experienced specialists in echocardiography
and, using two different echocardiographic systems. Systolic
and diastolic blood pressure and average heart rate were
measured at both examinations. The systolic ejection frac-
tion could be evaluated in all patients but in order to evalu-
ate the different diastolic parameters, the patient had to be
in sinus rhythm on both occasions, no atrial fibrillation in
the meantime, no or mild valve disease and having a normal
ejection fraction (EF) > 50%. The flowchart for all 298
patients, eligible for participation in the study is presented
in Figure 1. A total of 99 patients had atrial fibrillation at
the echocardiographic and/or during the ablation procedure,
seven patients had atrial flutter, nine patients had other
arrhythmias or pacemaker rhythm, eight patients had EF
/ C20 50%, and two patients had significant valve disease
( / C21 grade 2). In 35 patients, the invasive curves were missing or of
poor quality and in 12 patients, the non-invasive tissue-
doppler were missing. These patients were excluded from
the study. The remaining 125 patients (85 men; mean age
62.2 ± 11.1 years) had a normal ejection fraction > 50%,
sinus rhythm and no or only mild valve impairment, were
included to fulfill the study protocol and constituted the
study population. The study was approved by the Authority
of ethical approval, region Uppsala, (Dnr 2019-00034, Dnr
2020-02242) and a written informed consent was obtained
from all patients.

**Echocardiographic system and analysis**
The ultrasound system used for the transthoracic echocar-
diographic examinations of the study group was a commer-
cially available Vivid E 95, GE Healthcare, Horten Norway
or an Acuson SC 2000, Siemens Germany, using a
2.5–5 MHz transducer. All measurements were performed
using the incorporated calculation program in the ultra-
sound machines. The a’ velocity in the tissue-Doppler was
measured (cm/s) from septal and lateral annulus in the AV-
plane in the 4-chamber view and the average a’ = (septal a’
+lateral a’)/2 was calculated. The maximal velocity of the
pulmonary vein inflow into the left atrium during systole
(S) and diastole (D) was recorded (cm/s) was measured
with the sample volume placed 4–5 mm into the pulmonary
vein and the S/D ratio was calculated. The maximum tricus-
pid regurgitation (TR) velocity in the regurgitation jet

![Flowchart for included patients.](Figure 1)
between the right ventricle and the right atrium in the 4 chamber view was measured (m/s). The left atrial volume was estimated from the 4 chamber and 2 chamber view using the area-length method with correction for the body surface area [14]. The individual diastolic parameters in the ASE/EACVI-guidelines; e' velocity, E/e' ratio, LA volume index and maximum tricuspid regurgitation velocity were measured [1,2]. The ejection fraction was used as a measure of left ventricular systolic function. A normal systolic function was defined as EF > 50% [15].

Methods for invasive catheter measurements

Procedure
All procedures were performed on uninterrupted novel oral anticoagulant (NOAC) treatment. The LA pressure measurement (mmHg) was carried out after the calibration of the hemodynamic system (using HemoBox – Sensis Vibe), whereas the transducer is placed perpendicular just 5 cm from the heart level. In our EP-laboratory we use AXIOM Sensis HEMO + EP System, Siemens Medical. The pressure calibration in order to obtain a correct pressure zero was performed before the transeptal puncture (TSP). In every procedure we performed two transeptal punctures and the LA pressure is measured at least 20 s after each puncture. Each measurement includes the high, low and mean value, given by the system. The average LA pressure of two measurements was used or the most reliable pressure curve if there was a significant difference in curve quality.

Pressure measurements
Mean LA pressure (mmHg) was calculated as average pressure of 4–6 consecutive beats by using the Sensis EP system. The LA pre-A pressure (mmHg) was measured manually, immediately before the A-wave as average pressure of 4–6 consecutive beats. Mean LA pressure and LA pre-A pressure were compared in each patient. The heart rate and the systolic and diastolic blood pressure were also taken. A mean LA pressure and LA pre-A pressure > 12 mmHg was considered abnormally elevated [4]

Reproducibility
In 25 patients, we tested the intra-class correlation coefficients (ICC) in mean LAP and pre-A pressure between the two measurements performed in each patient. The ICCs were 0.994 (0.986, 0.997) resp 0.984 (0.963, 0.993). A high intra-observer and inter-observer correlation coefficients of 0.944–0.982 respective 0.927–0.983 between measurements for septal, lateral á velocity and the S/D ratio at two different occasions have been validated in a previous study [5].

Statistics
In order to describe the population we used descriptive statistics, absolute and relative frequencies for binary data, while mean and standard deviations were used for continuous data. Comparisons were performed by using Fisher’s exact test or the t-test for binary and continuous data respectively (Table 1). Description of groups based on mean LA pressure includes mean and standard deviation, and comparisons with t-tests (Table 2). To evaluate the dependence between tissue velocities and mean LA pressure we used the Pearson correlation coefficient with 95% confidence intervals, complemented with curves computed using a running line smoother with default bandwidth (Stata command roctab, Figure 3). To compute the optimal cut-off point in the ROC curve (Figure 3), we used the point where the Youden's index is maximum [16]. Intra class correlation coefficients (ICC) was used to evaluate the reproducibility of pre-A mean LA pressure, and mean LA pressure. The ICCs were calculated using a two-way mixed model for absolute agreement [17], and we used the bounds given by Cicchetti [18] for the interpretation (where values above 0.75 are considered excellent). All statistical analysis performed using Stata MP/4, version 16.1, and all tests were two-sided with significance level 0.05.

Results
One hundred and twenty-five patients were included in the study. The heart rate (58.5 ± 8.4 vs 57.6 ± 10.1; p = 0.43) and the diastolic blood pressure (82.8 ± 9.8 mmHg vs 81.6 ± 11.6 mmHg; p = 0.30) did not differ significantly between the echo-Doppler examination and the invasive measurement of mean LAP but the systolic blood pressure was higher during the echo-Doppler examination (144.4 ± 19.5 mmHg vs 138.9 ± 17.5 mmHg; p = 0.02).

As seen in table 2D, there was a positive correlation between mean LAP and pre-A pressure (r = 0.966). Twenty-six out of the 30 patients with elevated LAP had elevated LA pre-A filling pressure, and one patient with a normal

### Table 1. Baseline characteristics in the study population stratified for mean LA pressure ≤12 or >12 mmHg.

| Patients (n) | Mean LA pressure ≤12 mmHg | Mean LA pressure >12 mmHg | p Value |
|-------------|--------------------------|--------------------------|--------|
| Age, mean ± SD | 62.0 (11.2) | 66.7 (8.3) | ns |
| Male, n (%) | 65 (68.4) | 18 (60) | ns |
| Risk factors |
| Smokers, n (%) | 4 (4.2) | 2 (6.7) | ns |
| Hypertension, n (%) | 53 (53.8) | 20 (66.7) | ns |
| Diabetes mellitus, n (%) | 8 (8.4) | 2 (6.7) | ns |
| Hyperlipidemia, n (%) | 20 (21.1) | 6 (20) | ns |
| Previous AML, n (%) | 2 (2.1) | 3 (10.0) | ns |
| Previous CABG, n (%) | 1 (1.1) | 0 (0) | ns |
| Previous PCI, n (%) | 3 (3.2) | 4 (13.4) | ns |
| Stroke, n (%) | 1 (1.1) | 2 (6.7) | ns |
| Heart failure, n (%) | 11 (11.6) | 1 (3.3) | ns |

AML: acute myocardial infarction; CABG: Coronary Artery Bypass Grafting; PCI: Percutan Coronar Intervention.
The assessment of left ventricular systolic and diastolic function in the study population stratified for mean LA pressure ≤12 or >12 mmHg.

| Patients (n) | Mean LA pressure ≤12 mmHg | Mean LA pressure >12 mmHg | p Value |
|-------------|---------------------------|---------------------------|---------|
| Left atrial pressure (mmHg) | 95 | 30 | 8.7 ± 2.2 | 17.1 ± 4.6 | <.001 |
| Left ventricle | | | | | |
| Septal wall (mm) | 10.6 ± 1.5 | 10.6 ± 1.9 | .977 |
| Posterior wall (mm) | 9.8 ± 1.8 | 9.8 ± 1.8 | .705 |
| LVEDD (mm) | 50.5 ± 5.0 | 51.6 ± 5.0 | .273 |
| LVESD (mm) | 31.1 ± 4.8 | 30.4 ± 5.6 | .525 |
| Ejection fraction (%) | 60.3 ± 3.1 | 60.5 ± 3.6 | .789 |

*Continuous data as mean ± SD; E: diastolic early transmitral flow velocity; A: atrial diastolic transmitral flow velocity; E/A-ratio: early diastolic transmitral flow velocity/atrial diastolic transmitral flow velocity; DT: deceleration time of the E-wave; EDD: end diastolic RV diameter in 4 chamber view; TAM: tricuspid amplitude motion; TR: tricuspid regurgitation; LVESD: LV end-systolic dimensions; LVEF: left ventricular ejection fraction; a velocity: tissue-Doppler velocity in RV plane in 4 chamber view.*

LAP had elevated LA pre-A filling pressure. As seen in Figure 2(A–C) there is a negative correlation between mean LAP and septal a’ velocity ($r = -0.435$), lateral a’ velocity ($r = -0.473$) and average a’ velocity ($r = -0.491$).

Tables 1 and 2 show the characteristics and the assessment of left ventricular systolic and diastolic function stratified for mean LAP ≤12 or >12 mmHg. Figure 4 shows an illustration of a’ velocity in these two patient groups. A normal mean LAP (≤12 mmHg) was observed in 95 patients and an elevated mean LAP (>12 mmHg) in 30 patients. The patients with elevated mean LAP had lower septal a’ velocity (6.5 ± 2.7 vs 8.6 ± 2.3; $p < .01$), lateral a’ velocity (5.9 ± 2.3 vs 8.6 ± 2.1; $p < .01$) and average a’ velocity (6.2 ± 2.4 vs 8.8 ± 2.1; $p < .01$) compared to patients with normal mean LAP. No significant difference was noticed in the ejection fraction between the two groups. Using ROC curve analysis (Figure 3), septal a’, lateral a’ and average a’ velocity yielded an AUC of 0.78, 0.83 and 0.82 for prediction of elevated mean LAP. Optimal cut-off point to predict elevated mean LAP for average a’ velocity was 7.25 cm/s using Youden’s index with a sensitivity of 83% and a specificity of 78%.

Discussion

To diagnose patients with HFP EF still remains a significant clinical issue and new tools have been requested [3] but where are those to be found apart from the criteria in the current guidelines?

This is the first study ever published showing a good correlation between a direct measurement of left atrial contractile status using the parameter a’ velocity by tissue-Doppler echocardiography and invasively measured mean LAP, in patients with normal ejection fraction. The a’ velocity correlated well to mean LAP and there was a progressive decrease in a’ velocity as the mean LAP increased leading to highly significant lower a’ velocity in patients with elevated mean LAP. Furthermore, a’ velocity was a good indicator of elevated mean LAP with an AUC of 0.78-0.83 and average a’ velocity with cut-off < 7.25 cm/s detected 83% of all patients with elevated mean LAP, with a specificity of 77%. Interestingly, E/e’ ratio with cut-off > 14 had a very high specificity of 99% but a very low sensitivity of 6.7%. To ensure that elevated mean LAP was correlated to elevated LV filling pressure and not a consequence of a failing left atrium per se, we also measured LA pre-A pressure which should be a good indicator of the LV pre-A filling pressure and the correlation was excellent between these two parameters.

Our results indicates that a direct parameter of left atrial contractile status, a’ velocity could be a simple, robust and easily eligible parameter to detect a failing left atrium which is a good indicator of elevated filling pressures invasively. These findings could be of interest since studies in HFP EF patients have shown a decreased a’ velocity, LA contraction and LA strain, and an increased 10-year mortality, in patients with elevated pulmonary capillary wedge pressure (PCWP), thus, an assessment of LV filling pressures including a’ velocity could have additional information in guiding the medical therapy [11,19,20].

Limitation of the study

There are several limitations, which have to be considered. This is a retrospective study with its known limitations. Invasive and non-invasive assessments were not simultaneously recorded. The number of patients with increased mean left atrial filling pressure was low. This is a single-center study in an ablation population and therefore the results cannot be generalized to other patient populations with normal ejection fraction and suspected clinical heart failure.

Conclusion

The a’ velocity is a good indicator of mean LAP and might be considered in the evaluation of elevated left ventricle filling pressure in patients with normal ejection fraction.
Figure 2. (A–D) The correlation between mean LAP and septal a’ velocity (A), lateral a’ velocity (B), average a’ velocity (C) and pre-A LAP (D).

Figure 3. Receiver operating characteristics curves analysis for septal, lateral and average a’ velocity in predicting an increased mean LAP (>12 mm Hg). The optimal cut-off point for average a’ velocity according to Youden is indicated with a blue dot and the sensitivity, specificity and the cut-off value in this point is seen in the left square in the figure.
Figure 4. Illustrations showing $a'$ velocity in the tissue-Doppler of both basal-septal LV and basal-lateral LV for a representative patient with normal LAP $\leq 12$ mmHg (A–B) and for patient with elevated LAP $>12$ mm Hg (C–D).

| Table 3. The sensitivity, specificity and accuracy of $a'$ velocity to detect an increased mean LAP ($>12$ mmHg) using different cut-off values compared to E/e' ratio $>14$ cut-off. |
|---------------------------------------------------------------|
| Cut-off $< 6$ cm/s  | Sensitivity, % [95% CI] | Specificity, % [95% CI] | Accuracy, % [95% CI] |
| Septal $a'$ velocity | 36.7 [19.9, 56.1] | 94.7 [88.1, 98.3] | 80.8 [72.8, 87.3] |
| Lateral $a'$ velocity | 62.1 [40.6, 77.3] | 89.5 [81.5, 94.8] | 82.4 [74.6, 88.6] |
| Average $a'$ velocity | 55.2 [34.3, 71.7] | 92.6 [85.4, 97.0] | 83.2 [75.5, 89.3] |
| Cut-off $< 8$ cm/s  | Sensitivity, % [95% CI] | Specificity, % [95% CI] | Accuracy, % [95% CI] |
| Septal $a'$ velocity | 73.3 [54.1, 87.7] | 69.5 [59.2, 78.5] | 70.4 [61.6, 78.2] |
| Lateral $a'$ velocity | 82.8 [61.4, 92.3] | 70.2 [60.1, 79.4] | 73.2 [64.1, 80.4] |
| Average $a'$ velocity | 82.8 [61.4, 92.3] | 74.5 [60.8, 79.7] | 76.4 [64.5, 80.9] |
| Cut-off $< 10$ cm/s | Sensitivity, % [95% CI] | Specificity, % [95% CI] | Accuracy, % [95% CI] |
| Septal $a'$ velocity | 93.3 [73.5, 97.9] | 35.8 [26.2, 46.3] | 48.8 [39.8, 57.9] |
| Lateral $a'$ velocity | 89.7 [69.3, 96.2] | 38.9 [29.1, 49.5] | 50.4 [41.3, 59.5] |
| Average $a'$ velocity | 96.0 [73.5, 97.9] | 31.6 [22.4, 41.9] | 45.6 [36.7, 54.7] |
| Cut-off $< 7.25$ cm/s | Sensitivity, % [95% CI] | Specificity, % [95% CI] | Accuracy, % [95% CI] |
| Average $a'$ velocity | 82.8 [64.2, 94.2] | 77.2 [67.2, 85.3] | 78.5 [70.1, 85.5] |
| E/e' ratio $>14$ cut-off | 6.7 [0.8, 22.1] | 98.9 [94.2, 100.0] | 76.6 [68.2, 83.7] |
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