# The time interval between the onset of tricuspid E wave and annular Ea wave ($T_{E\text{-}Ea}$) can predict right atrial pressure in patients with heart failure

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## ABSTRACT

**Objective:** There is conflicting data regarding the tricuspid annular velocities and their relation to right ventricular filling pressures. We aimed to assess if the time interval between the onset of tricuspid E wave and annular Ea wave has any correlation with right sided filling pressure in patients with heart failure.

**Methods:** Thirty heart failure patients (left ventricular ejection fraction≤35%) were enrolled. Echocardiography was performed to obtain tricuspid inflow and tissue Doppler annular velocities just before a standard right heart catheterization. The right atrial pressure was obtained from right heart catheterization. The E/Ea [the ratio of peak velocity of early tricuspid inflow wave (E) to peak velocity of early diastolic wave of the lateral tricuspid annulus (Ea)] and the time intervals between the beginning of R wave of electrocardiogram and onset of E (TE) as well as between the beginning of R wave and onset of Et ($T_{Ea}$) were measured, $T_{E\text{-}Ea}$ was calculated as $T_{E\text{-}TEa}$.

**Results:** The mean right atrial pressure (RAP) was 8.8 (SD=4.7) mm Hg. The mean $T_{E\text{-}Ea}$ was + 8.61 milliseconds. There was no significant correlation between RAP and E/Ea (r=0.08, p>0.05) but the correlation between $T_{E\text{-}Ea}$ and RAP was significant (r=0.5, p=0.01).

**Conclusion:** According to our results and in contrary to some prior studies, we showed for the first time that right side $T_{E\text{-}Ea}$ stands as a better surrogate of right atrial pressure than E/Ea in heart failure patients. This finding needs more accurate studies and could present $T_{E\text{-}Ea}$ as a feasible tool to look into hemodynamics of heart failure patients. *(Anadolu Kardiyol Derg 2014; 14: 585-90)*

**Key words:** heart failure, Doppler echocardiography, right heart catheterization

## Introduction

The estimation of right heart filling pressure is important clinically for the diagnosis and management of various hemodynamic conditions. Furthermore, to estimate systolic right ventricular and pulmonary artery pressures in the echocardiography laboratory assessment of right atrial pressure (RAP) is needed (1). An accurate estimation of RAP is of paramount importance to obtain more reliable noninvasive evaluations of pulmonary pressures. The most frequently used technique for its estimation is the observation of the diameter and collapsibility of the inferior vena cava (1, 2). By tissue Doppler (TD) imaging technique the recording of myocardial and annular velocities is possible. The early diastolic mitral annular velocity (Ea) has been used to assess the left ventricular (LV) relaxation, and predict LV filling pressures in a number of different populations (3-8). However, there is conflicting data regarding the tricuspid annular velocities and their relation to right ventricular (RV) filling pressures (9-16). It could be assumed that like left side the presence of regurgitations and stenoses affect the velocities of tricuspid inflow. Unlike velocities, certain time intervals can be less prone to the confounding effect of the aforementioned hemodynamic variables (17, 18). In that regard, investigators have previously reported on a novel time interval for the assessment of LV relaxation, namely, the interval between the onset of mitral E and annular Ea, $T_{E\text{-}Ea}$, which is well related to the time constant of LV relaxation and left atrial (LA) pressure in canine and clinical studies (17, 18). Earlier studies noted that, in normal individuals the peak velocity of Ea and transmitral early diastolic velocity (mitral E) occur almost simultaneously, whereas in patients with restrictive cardiomyopathy and animal model of pacing-induced heart failure, the peak velocity of Ea occurs after that of transmitral early diastolic velocity (mitral E) (17-19). It has been shown that when LV relaxes, mitral annulus moves first and the velocity of annulus is the first one detected by TD imaging and mitral inflow velocity being detected shortly after that by Doppler.

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In normal individuals, this time interval is very short and the Ea comes early, especially on right side of the heart (17-19). In this regard, it could be postulated that if atrial pressure reaches to a very high level, blood would force the atrio-ventricular valve to open sometime earlier than with annular motion, causing the E to come earlier than Ea and the time interval to increase.

We aimed to assess if this time interval at tricuspid level has any correlation with right sided filling pressure in patients with heart failure.

## Methods

### Study population

Thirty heart failure patients were enrolled according to the following inclusion criteria: ischemic and/or dilated cardiomyopathy with severe left ventricular (LV) systolic dysfunction [LV ejection fraction (EF) ≤35%], a New York Heart Association (NYHA) functional class II-III. optimal medical treatment with diuretics and neurohormonal blockers according to latest guidelines on HF management (20) for at least 3 weeks, and normal sinus rhythm. The exclusion criteria comprised of atrial fibrillation or any other arrhythmias confounding the echocardiographic measurements, acute heart failure state, stage D heart failure, inotropic treatment, history of previous cardiac surgery such as coronary artery bypass grafting and any valvular surgery, advanced documented pulmonary diseases, and inadequate echocardiographic window.

The study was reviewed and approved by the Ethics Committee at Rajaie Cardiovascular Medical and Research Center, and written informed consent was obtained from all the patients.

### Right heart catheterization

The right heart catheterization was performed by standard method in all patients using 7F balloon-tipped, triple lumen thermodilution catheters (Edwards Lifesciences Corporation, USA) and Vigilance (VGSVSYS) monitors (Edwards Lifesciences Corporation, USA) in the catheterization laboratory. All the measurements were obtained with the patients at rest in the supine position, breathing room air. The pressures were all averaged in three consecutive heart beats at end-expiration. The following variables were measured for each patient: pulmonary capillary wedge pressure (PCWP); systolic, diastolic, and mean pulmonary artery pressure; systolic and end-diastolic right ventricular (RV) pressure; mean right atrial pressure; mixed venous oxygen saturation and cardiac output via the thermodilution technique.

### Echocardiographic study

A comprehensive two-dimensional (2D) color Doppler echocardiography was performed in each patient using a commercial GE Vivid 7 with a 3-MS variable frequency harmonic phased array transducer just before performing right heart catheterization.

The LV global systolic function was evaluated in terms of the ejection fraction (EF), employing the biplane modified Simpson method. The RV systolic function was evaluated in accordance with the American Society of Echocardiography guidelines (1) for the echocardiographic assessment of the right heart in adults using the following parameters: tricuspid annular plane systolic excursion(TAPSE) and tissue Doppler-derived tricuspid lateral annular systolic velocity (S'). TAPSE <16 mm, and S' velocity <10 cm/s indicated RV systolic dysfunction. The RA area was measured at the end-systole in the four-chamber view. The tricuspid regurgitation (TR) severity was also assessed in accordance with the American Society of echocardiography guidelines (1).

All Doppler values represent the average of three beats and were obtained during breath hold at end-expiration. Tricuspid inflow was analyzed for peak E, peak A velocities, E/A ratio. The tissue Doppler Ea and Aa velocities at tricuspid annulus in four-chamber view were measured, and the ratio E/Ea was computed. In addition, the time intervals between the beginning of R wave and onset of tricuspid E velocity ($T_E$) as well as the time interval between the beginning of R wave and onset of Ea ($T_{Ea}$) at the tricuspid annulus were measured. The R-R intervals used for timing the onset of tricuspid E and Ea were identical. Subsequently, the $T_{E-Ea}$ was computed by subtracting $T_E$ and $T_{Ea}$ (Fig. 1).

### Measuring the reliability

Inter-observer variability were calculated as the absolute difference divided by the average of the two observations for all the parameters. Fifteen cases were analyzed for the calculation of the interobserver variability.

### Statistical analysis

All the analyses were conducted using SPSS® 15 for Windows® (SPSS Corp, Chicago, IL, USA). The unpaired Student t-test was performed for the continuous variables. Data pre-

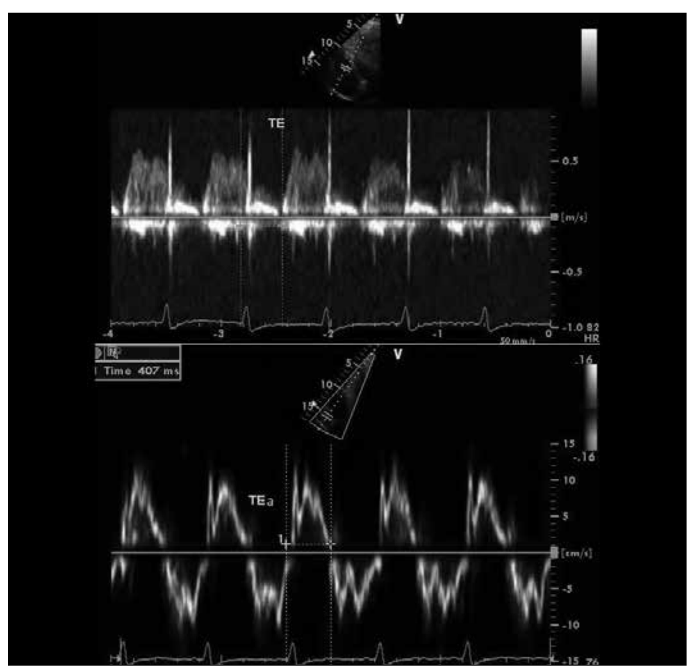


**Figure 1. Upper, mitral inflow Doppler imaging. Lower, TDI recording at tricuspid annulus in four chamber view in patients with heart failure, the time intervals between the beginning of R wave and onset of tricuspid E velocity as well as the time interval between the beginning of R wave and onset of Ea at the tricuspid annulus were measured**

sented as mean±standard deviation (SD) for interval and count (percent) for categorical variables. One sample Kolmogorov-Smirnov test was used to show the fitness of interval variables with Gaussian distribution. Comparisons between right atrial pressures (RAP) in the study sub-groups were performed by Studentıs t test or one-way ANOVA model. The Pearson correlation coefficient (r) was utilized to show the correlations between several echocardiographic and hemodynamic findings. Adjusted associations between RAP and other factors were investigated by multiple linear regression models. Validity of $T_{E-Ea}$ index to diagnose high right atrial pressure was assessed by receiver operative characteristics (ROC) curve analysis.

A p value of 0.05 was considered statistically significant.

## Results

A total of 30 heart failure patients, consisting of 22 dilated and 8 ischemic cardiomyopathies were included in the present study. Table 1 depicts the general characteristics and Table 2 demonstrates the right-heart catheterization and echocardiographic data of the study population. The interobserver variability for both E/Ea and $T_{E-Ea}$ was 5±2%.

The mean RA pressure was 8.8±4.7 mm Hg and the mean PAP, mean PCWP and mean cardiac output were 28.8±14.5 mm Hg, 19.8±10.7 mm Hg and 4.2±1.1 Lit/min respectively.

The patients had a mean LVEF of 21.2±6.5% and regarding right ventricular function the mean of S' and TAPSE were 9.5±2.7 cm/sec and 15.7±3.7 mm respectively.

The mean $T_{E-Ea}$ was + 8.61 msec [a minimum of -100 msec and a maximum of +120 msec with a mean (SD) of 8.61(55) msec], in heart failure patients which showed E is the first velocity detected by Doppler.

Correlations between the right atrial pressure and other echocardiographic or catheterization indices are presented in Table 3. Also, associations between RAP and some patients' background factors, IV C collapse and tricuspid regurgitation severity are shown in Table 4. There was no significant correlation between RAP and E/Ea in heart failure patients (r=0.08, p>0.05) but the correlation between $T_{E-Ea}$ and RA pressure was significant (r=0.47, p=0.01). As shown in the studies on the left heart, the left $T_{E-Ea}$ could be considered as a better index for the estimation of left atrial pressure in the patients with significant mitral regurgitation. Assuming the same physiology for the right side of the heart, adjusted association between right atrial pressure and TR severity was investigated by regression model and confirmed this significant correlation with following formula for calculation RA pressure in patients with heart failure based on $T_{E-Ea}$: RA pressure=[6.3+0.03($T_{E-Ea}$)] + 5.2 (TR severity ≥moderate) (Table 5).TR severity value is 0 if TR severity is less than moderate and 1 if the TR severity is at least moderate (Fig. 2).

The agreement between the estimated values for RAP, using the above-mentioned model and observed values is shown in a Bland-Altman plot (Fig. 3).

There was also a good association between IVC collapse and $T_{E-Ea}$ (p=0.004) but not with E/Ea (p value >0.05) in our heart failure patients.

**Table 1. Participants' general characteristics (n=30)**

| Variable | Descriptive index |
|---|---|
| Age, years | 39±15 |
| Sex, M/F | 24/6 |
| BSA, m$^2$ | 1.69±0.13 |
| Systolic BP, mm Hg | 107.5±20 |
| Diastolic BP, mm Hg | 68±10 |
| Heart rate, beat/min | 84±12 |

Values are presented as mean± SD
BP - blood pressure; BSA - body surface area; F - female; M - male

**Table 2. Echocardiography and right-heart catheterization findings in the heart failure patients (n=30)**

| Index | Mean (SD) |
|---|---|
| LVEF | 21.2 (6.5) |
| RAA index | 11.2 (5.5) |
| IVC size | 18.1 (6) |
| RVSm | 9.5 (2.7) |
| TAPSE | 15.7 (3.7) |
| RVEDD | 31.5 (13.9) |
| Right E/A | 1.5 (0.9) |
| Right E/Ea | 5.9 (3.2) |
| Right T E-Ea | 8.61 (55) |
| TRG | 40 (21) |
| Echo PAP | 53.2 (25) |
| Mean RA pressure | 8.8 (4.7) |
| RVSP | 43.7 (22.4) |
| RVEDP | 9.3 (3.9) |
| SPAP | 43.7 (22.6) |
| DPAP | 21 (11) |
| Mean PAP | 28.8 (14.5) |
| PCWP | 19.9 (10.7) |
| CO, thermodilution | 4.2 (1.1) |
| CI, thermodilution | 2.4 (0.6) |

CO - cardiac output; CI - cardiac index; DPAP - diastolic pulmonary artery pressure; IVC - inferior vena cava; LVEF - left ventricular ejection fraction; PAP - pulmonary artery pressure; PCWP - pulmonary capillary wedge pressure; RA - right atrium; RAA - right atrial area; RV - right ventricle; RVEDD - right ventricular end diastolic diameter; RVEDP - right ventricular end diastolic pressure; RVSP - right ventricular systolic pressure; SPAP - systolic pulmonary artery pressure; TAPSE - tricuspid annular plane systolic excursion; TRG - tricuspid regurgitation gradient

According to ROC curve analysis, $T_{E-Ea}$ could be a high validity measure to diagnose right atrial pressure ≥ 8 mm Hg. Area under the ROC curve (AUC) was 0.873 (CI95%: 0.737-1.00), p value <0.001 (Fig. 4). Sensitivity and specificity of the diagnosis are presented in table 6 for several cut-points. For example, the value about ≥8 msec for $T_{E-Ea}$, showed a sensitivity of 0.813 and a specificity of 0.846 for the diagnosis of RAP ≥8 mm Hg.

**Table 3. Correlations between the right atrial pressure and other echocardiographic or catheterization indices**

| Index | r* | *P* |
|---|---|---|
| RAA, index | 0.188 | 0.329 |
| IVC size, mm | 0.471 | 0.010 |
| RV S′ | -0.208 | 0.278 |
| TAPSE | -0.566 | 0.001 |
| RVEDD | 0.300 | 0.113 |
| E | 0.523 | 0.004 |
| A | -0.278 | 0.144 |
| Ea | 0.379 | 0.043 |
| Aa | -0.329 | 0.081 |
| E/A | 0.441 | 0.017 |
| Ea/Aa | 0.530 | 0.003 |
| E/Ea | 0.081 | 0.676 |
| T E-Ea | 0.471 | 0.010 |
| TRG | 0.313 | 0.098 |
| EchoPAP | 0.375 | 0.045 |
| RV SP | 0.606 | <0.001 |
| RVEDP | 0.859 | <0.001 |
| SPAP | 0.606 | <0.001 |
| DPAP | 0.663 | <0.001 |
| Mean PAP | 0.652 | <0.001 |
| PCWP | 0.625 | <0.001 |
| CO (Therm) | -0.321 | 0.090 |
| CI (Therm) | -0.381 | 0.041 |

*r - Pearson's correlation coefficient
CI - cardiac index; CO - cardiac output; DPAP - diastolic pulmonary artery pressure; IVC - inferior vena cava; LVEF - left ventricular ejection fraction; PAP - pulmonary artery pressure; PCWP - pulmonary capillary wedge pressure; RA - right atrium; RAA - right atrial area; RV - right ventricle; RVEDD - right ventricular end diastolic diameter; RVEDP - right ventricular end diastolic pressure; RVSP - right ventricular systolic pressure; SPAP - systolic pulmonary artery pressure; TAPSE - tricuspid annular plane systolic excursion; Therm-thermodilation; TRG - tricuspid regurgitation gradient

## Discussion

According to our study, which up to our knowledge has been the first ever study applying the time interval between the onset of Tricuspid E wave and annular Ea wave ($T_{E-Ea}$), we found a significant positive correlation between $T_{E-Ea}$ and RAP along with no significant correlation between RA pressure and E/Ea.

There is conflicting data regarding the tricuspid annular velocities and their relation to right ventricular (RV) filling pressures. Using transthoracic echocardiography, investigators have looked into the correlation between the right E/Ea ratio [the ratio of tricuspid peak early inflow velocity (E) to peak early diastolic velocity of the lateral tricuspid annulus (Ea)] and right atrial (RA) pressure in cardiovascular patients come to different results.

Sundereswaran et al. (11), evaluated 50 cardiac transplant patients and found that the tricuspid E velocity was directly related to right atrial pressure; whereas Ea of the tricuspid annulus had no significant correlation. They also showed a good correlation between the tricuspid E/Ea and right-sided filling pressures.

In a similar investigation, Hanifah et al. (9) concluded that a cut-off value of E/Ea more than 3.95 could predict right atrial pressure ≥ 10 mm Hg measured by a central venous line (sensitivity: 73.1%; specificity: 70.8%; positive predictive value: 73% and negative predictive value: 73.9%) in a mixed group of patients in a Cardiovascular Care Unit.

Nageh et al. (10) validated the correlation between the right E/Ea ratio and right atrial (RA) pressure in a mixed group of

**Table 4. Comparison of right atrial pressure in different sub-groups of study participants**

| | RAP (mean±SD) | *P* |
|---|---|---|
| **Gender** | | 0.061 |
| Female (n=6) | 5.2±1.8 | |
| Male (n=24) | 9.5±4.8 | |
| **Diagnosis** | | 0.175 |
| DCM (n=22) | 8±3.6 | |
| ICM (n=8) | 10.8±6.9 | |
| **IVC collapse** | | |
| no collapse (n=14) | 10.7±5.6 | |
| <50% (n=6) | 8.4±3.6 | |
| >=50% (n=10) | 6.3±2.5 | |
| | 0.074 | |
| **TR severity** | | <0.001 |
| No/mild (n=18) | 6.4±2.6 | |
| Moderate/ Severe (n=12) | 12.3±5 | |

DCM - dilated cardiomyopathy; ICM - ischemic cardiomyopathy; IVC - inferior vena cava; RAP - right atrial pressure

**Table 5. Regression model to investigate adjusted association between right atrial pressure and other determinants***

| | Coefficient | SE | *P* |
|---|---|---|---|
| Constant | 6.332 | .825 | <.001 |
| TR severity[†] | 5.284 | 1.302 | <.001 |
| TE-Ea | .032 | .012 | .011 |

*: Model $r^2$=0.524
[†]: Tricuspid regurgitation no or mild against moderate to severe

**Table 6. Comparison of the validity for different cut-points of TE-Ea to determine right atrial pressure ≥8 mm Hg**

| Cut-point | Sensitivity | Specificity |
|---|---|---|
| 3.50 | .875 | 0.769 |
| 8.00 | .813 | 0.846 |
| 10.80 | .750 | 0.846 |
| 14.30 | .688 | 0.846 |
| 18.50 | .625 | 0.846 |
| 26.50 | .625 | 0.923 |

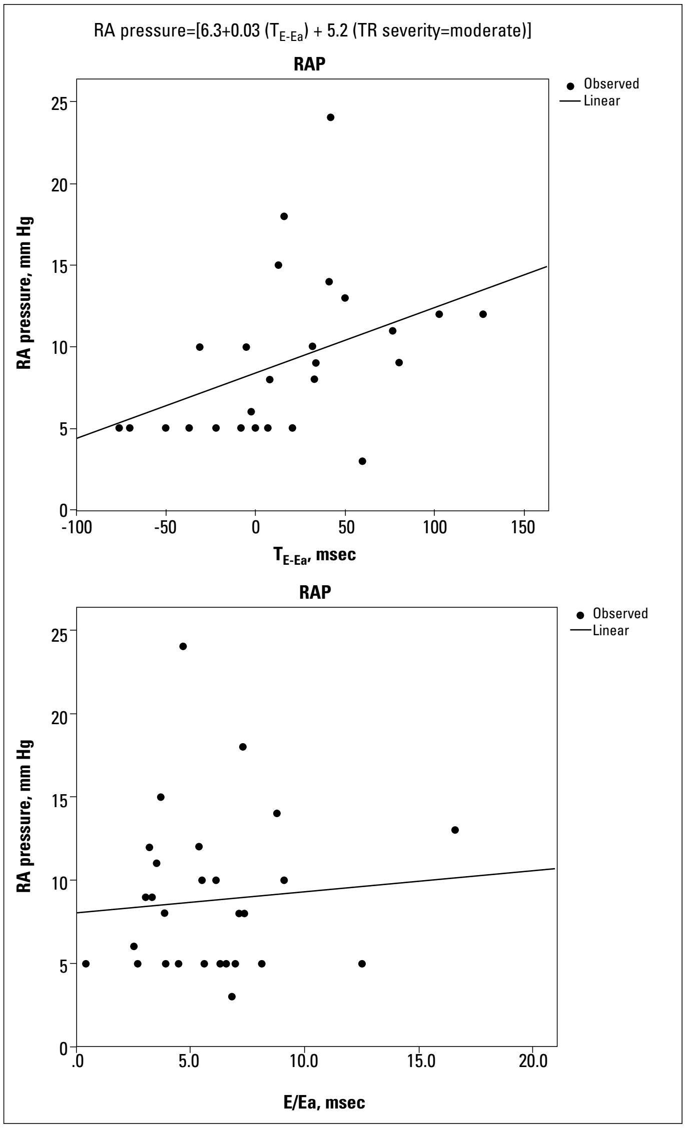


**Figure 2. Relation between Tricuspid TE-Ea (upper) versus E/Ea (lower) and mean right atrial pressure (RAP) in patients with heart failure**

spontaneously breathing and mechanically ventilated patients. They introduced tricuspid E/Ea ratio as a new index of RV filling pressures and concluded that mean RAP could be estimated fairly accurate in both patients with and without RV systolic dysfunction and/or mechanical ventilation using the tricuspid E/Ea ratio.

Said et al. (12), evaluated 50 patients in whom central venous catheters were inserted for cardiac and no cardiac indications (e.g., heart failure, hemodialysis) and concluded that among various echocardiographic variables including right E/A, Ea/Aa, E/Ea, and E/IVRT ,tricuspid annular E/Ea ratio is identified as the best index for noninvasive determination of RAP.

On the other hand, Michaux et al. (13) showed no correlation between right E/Ea and RAP in mechanically ventilated patients. They concluded that the E/Ea ratio failed to predict RA pressure in anesthetized, paralyzed, and mechanically ventilated patients because RA pressure would largely be influenced by extra car-

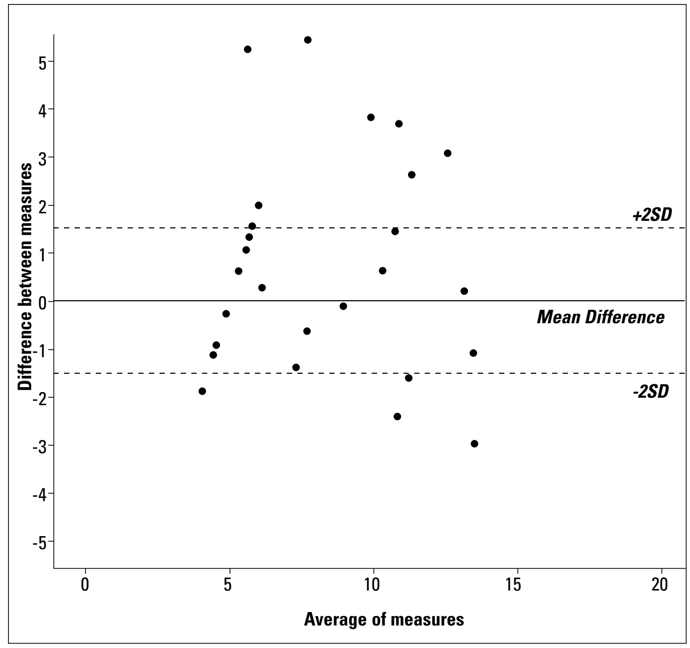


**Figure 3. Bland-Altman plot to show the agreement between observed right atrial pressure and estimated values by the linear regression equation**

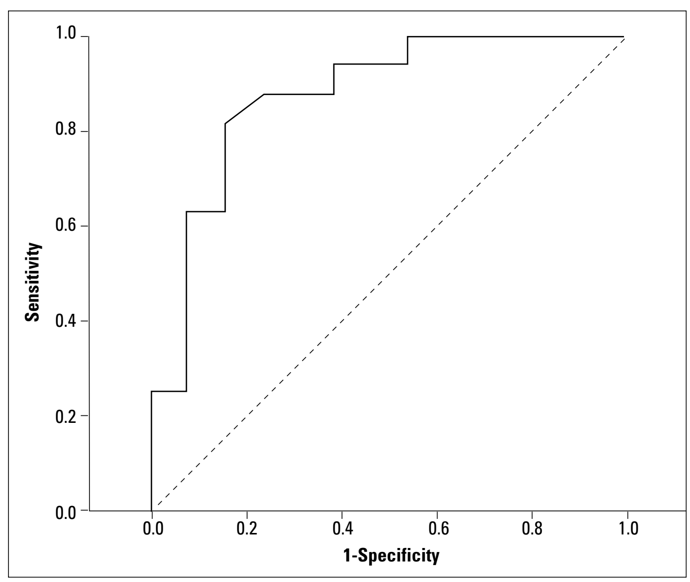


**Figure 4. Receiver operative characteristics (ROC) curve shows the good validity for $T_{E-Ea}$ index to determine right atrial pressure ≥8 mm Hg in study population**

[Area under the ROC curve was 0.873 (CI95%: 0.737-1.00), *P* value <0.001]

diac factors in these patients. Similarly, Yıldırımtürk et al. (14) showed no correlation between right E/Ea and RAP in patients with mitral stenosis with atrial fibrillation rhythm and /or normal sinus rhythm and Sade et al. (15) found that the right E/Ea was a weak correlate of RAP early after cardiac surgery and in patients with normal RV function.

Echocardiography derived time intervals have also fascinated many investigators in a try to find non-invasive surrogates of RAP. An inverse relationship was demonstrated between mean RAP and the interval between the end of the systolic annular motion to the onset of the early diastolic filling wave (right ventricular regional isovolumic relaxation time) by Abbas et al. (16).

It has been shown that normal individuals have the peak velocity of Ea and transmitral early diastolic velocity (mitral E) occurring almost at the same time, while in those with restricted physiology, mitral E comes earlier than annular Ea (17-19). Assuming a relatively same physiology in right side, we evaluated the relation of time interval of trans-tricuspid E and tricuspid annular E to the RAP. Considering the homogeneity of our patient population in contrary to Sundereswaran (11), Nageh (10) and Said (12), we believe that E/Ea could be misleading in heart failure settings. On the other hand, TE-Ea, which is easily measured by echocardiography, turned out to be in significant positive correlation to right atrial pressure even after adjustment the effect of TR severity. There might be many explanations for this: right ventricle, being known as the "volume chamber" of heart, exerts much less "afterload"-like effect on right atrium and results in a more liberal reply of tricuspid valve to increased right atrial pressure, which is earlier opening of tricuspid valve in an answer to increased right atrial pressure and hence an increased $T_{E\text{-}Ea}$.

## Study limitations

This study is in a small number of subjects. Further studies to better investigating the nature of right side $T_{E\text{-}Ea}$ seems mandatory in this regard.

## Conclusion

According to our results and in contrary to some prior studies, we showed for the first time that right side $T_{E\text{-}Ea}$ stands as a better surrogate of right atrial pressure than E/Ea in heart failure patients. This finding needs more accurate studies and could present $T_{E\text{-}Ea}$ as a feasible tool to look into hemodynamics of heart failure patients.

**Conflict of interest:** None declared.

**Peer-review:** Partially-external peer-reviewed.

**Authorship contributions:** Concept - N.N.; Design - A.A., H.B., M.E., N.N., Z.O.H.; Supervision - M.E., M.M., N.N., Z.O.H.; Resource - A.A., M.M., N.N., Z.O.H.; Materials - A.A., N.N., S.T.; Data collection &/or processing - A.A., N.N., S.T.; Analysis &/or interpretation - A.A., H.B., M.E., N.N.; Writing - A.A., H.B., M.E., N.N., Z.O.H.; Critical review - A.A., N.N.

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