Correlation of Left Atrial Electromechanical Delay with Left Atrial Function and Level of N-Terminal Pro B-Type Natriuretic Peptide in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Background: **In heart failure, atrial electromechanical delay (EMD) is frequently prolonged & may be associated with natriuretic peptide levels & left atrial function. Its function in HFpEF is still unknown & poorly understood, despite research on dilated cardiomyopathy** ***Aim:*** **To investigate the linkage between left atrial electromechanical delay (LA-EMD) & LA function with NT-proBNP levels in participants with HFpEF.** ***Methods:*** **Forty individuals exhibiting heart failure with preserved EF were recruited for this cross-sectional analysis. investigation, diagnosed in light of the most current ESC guidelines for HF. Eligible participants either had a H2FpEF score of ≥6 or a score of 3–5 accompanied by evidence of structural heart disease indicative of LV diastolic dysfunction, along with NT-proBNP levels exceeding 125 pg/mL.** ***Results:*** **No significant (P>0.05) correlation between (Nt-proBNp, LA-EMD, & left trial volumes & function) in all studied patients. A notable significant positive association between Nt-proBNp & each of E/A (r= 0.478), E/e' med (r= 0.912), E/e' lat (r= 0.876), E/e' AV (r= 0.915), TRV (r= 0.478), & PASP (r= 0.478). A significant negative correlation (r= -0.313) between Nt-proBNP & EDT in all studied patients. Statistical analysis demonstrated a significant positive association among cLA-EMD & TRV (r= 0.387), & EPASP (r= 0.435) in all patients studied. Analysis demonstrated a strong negative association (r = –0.582, P < 0.001) among cPA-MED & BMI in all studied patients.** ***Conclusions:*** **The findings revealed no evidence of a statistically significant connection between Nt-proBNp & left atrial electromechanical delay including cPA-lat, cPA-med & cLA-EMD. However, NT-proBNP levels is more strongly linked to diastolic function parameters like E/A & E/e` than to LA-EMD or Left atrial volumes & functions.**

Keywords: Left Atrial Electromechanical Delay, Left Atrial Function, Level of NT Pro BNP, PEF.

Introduction:

One well-known indicator of atrial remodeling & atrial fibrillation vulnerability is electromechanical delay (EMD), which is time gap between electrical activation & mechanical contraction of myocardium (1,2). By using tissue doppler imaging (TDI) in conjunction with electrocardiography, atrial EMD can be non-invasively measured by timing the onset of the A′ wave associated with atrial contraction on TDI with the appearance of the P wave on the ECG (3). Transthoracic echocardiography (TTE), with a focus on diastolic dysfunction & left atrial (LA) characteristics, continues to be the gold standard for diagnosing patients with heart failure with preserved ejection fraction (4). Evidence of diastolic dysfunction combined with adequate LV myocardial contractile activity confirms a diagnosis of HFpEF (5).

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There is little information on atrial conduction characteristics in HFpEF [6], despite the fact that LA mechanical performance is essential for preserving left ventricular filling in diastolic failure [6]. Prolonged atrial EMD has been associated in the past with decreased LV ejection fraction, increased LA volume, & higher natriuretic peptides. Nevertheless, nothing is known about the relationship between NT-proBNP levels, LA EMD, & LA function in HFpEF [8]. The purpose of this study is to assess these associations in patients with HFpEF.

Patients & Procedures: 40 male & female subjects over the age of 18 who met the diagnostic criteria for HFpEF, as stated in most recent HF guidelines by European Society of Cardiology (ESC) [9], scored ≥ 6 points on the H2PEF score or scored 3-5 points with evidence of structural cardiac abnormalities indicative of left ventricular diastolic dysfunction & NT-proBNP > 125 PG [10], were enrolled using an observational analytical cross-sectional approach. After receiving ethical approval from Suez Canal University Hospitals, the inquiry was conducted. Prior to their engagement in the study, all individuals provided written informed consent.

Patients who satisfied any of the exclusionary requirements listed below were not accepted: those who did not fit the criteria for HFpEF; those who had previously been diagnosed with coronary artery disease with abnormalities of the LV wall motion; LVEF below 50%; cardiac structural disorders, such as congenital heart disease & various forms of cardiomyopathy; or significant valvular disorders; & those who presented with poor quality echocardiographic & electrocardiographic imaging, multiple atrial tachycardia, atrial flutter, multiple atrial fibrillation, or electrocardiographic evidence of bundle branch block or atrioventricular conduction abnormalities. Every participant in the study had a thorough medical checkup, including a standard 12-lead electrocardiogram (ECG) recording & echocardiographic evaluation. LA function & volume were also assessed.

Left atrial volume & function

Volume of LA was measured during end-systole, which is the cardiac cycle phase immediately before the start of mitral inflow, & indexed to the patient's body surface area using the biplane area–length approach. The endocardial margins were clearly visible because to the use of echocardiographic pictures taken from the apical four- & two-chamber. By physically following the endocardial boundary & carefully excluding area under the mitral valve annulus, the pulmonary venous system, & the LA appendage, the maximal LA area was determined in both views. The vertical distance between the top of the LA roof & middle of the mitral valve's annular structure was known as LA length. LA volume was then computed using the standard equation:

LA Volume (AL) = 0.85 × (A4CH × A2CH)/ L, where L represents by averaging the two measured lengths [23].

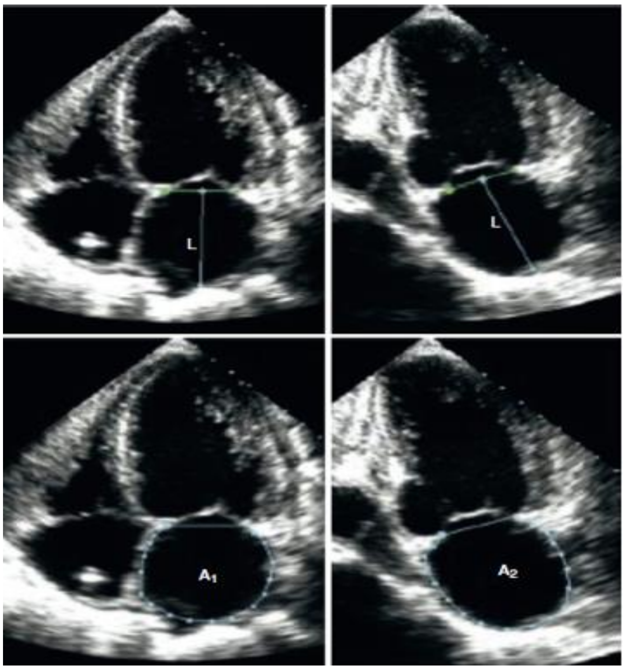


Figure 1: Biplane Disk Summation Method for Estimating LA Volume [23]

Left atrial (LA) foreshortening was ruled out by verifying a ≤5 mm variation in LA length between apical views in order to assure measurement reliability. The biplane area–length approach was used to assess the LA function. At the end of the T wave on the ECG & just before the mitral valve opened, the maximum LA volume (LAVmax) was recorded. At end of the diastole, the QRS complex began, & the mitral valve closed, the minimum LAVmin was measured. From the superior LA roof to the mitral annular plane, the LA longitudinal dimension was measured..

Volume calculation was performed using biplane area–length method based on images gathered from apical four- & two-chamber views, applying following formula:

LA total emptying volume= LAVmax – LAVmin

$$\text{LA total emptying fraction} = (\text{LAVmax} - \text{LAVmin})/\text{LAVmax}$$

Atrial Electromechanical delay & Tissue Doppler Imaging

Tissue Doppler imaging was performed with optimized gain & sweep speed (100–150 mm/s) to enhance myocardial velocity resolution. Pulsed-wave Doppler signals were obtained from lateral & septal mitral annuli in apical four-chamber view, with careful alignment to minimize insonation angle errors. Atrial electromechanical delay (PA interval) was measured from the onset of the P wave on ECG to start of the Am wave at each annular site. To control for heart rate variability, PA intervals were corrected using Bazett's formula [11]. Final left atrial EMD was calculated as difference between the corrected PA lateral & PA septal intervals, with measurements averaged over three consecutive cardiac cycles.

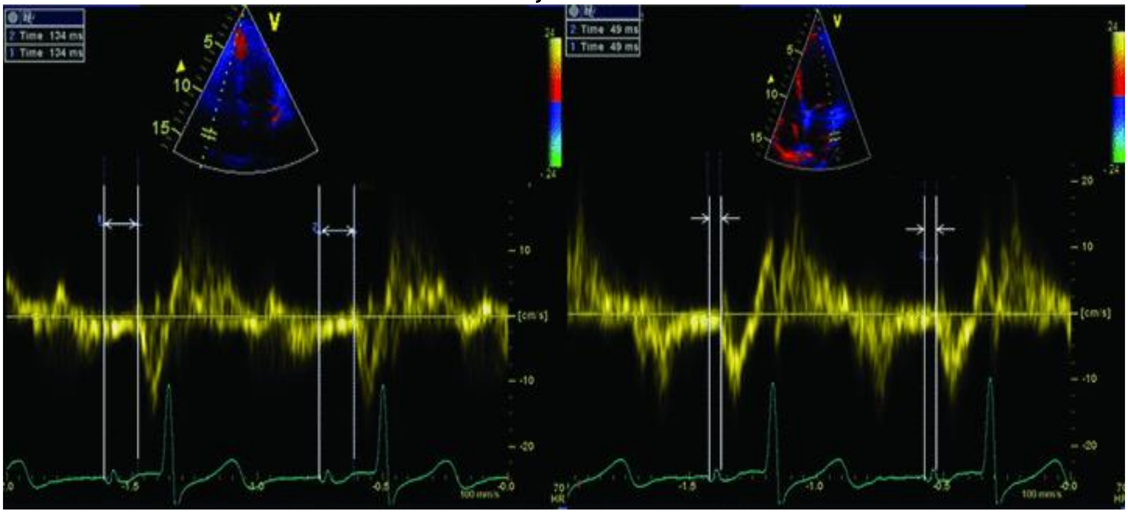


Figure 2: Pulsed-wave TDI measures atrial EMD at various atrial walls as the time between the pacing spike and tissue Doppler A′ wave.

BNP measurement

NT-proBNP was measured from venous blood obtained via cubital vein puncture, with samples collected in citrate tubes & analyzed using a standardized ELISA method. The human NT-proBNP ELISA kits employed had a detection threshold of 11.5 pg/mL. In accordance with established diagnostic criteria, heart failure was defined by NT-proBNP levels ≥125 pg/mL [10].

Statistical analysis

The data was analyzed using SPSS 26.0 (IBM Corp., Chicago, IL, USA). Categorical data were presented as frequencies and percentages, whereas quantitative variables were presented as mean ± SD. Pearson's correlation coefficient (r) assessed continuous variable correlations. Diagnostic performance of each predictor was assessed using ROC curve analysis to determine sensitivity and specificity. Multivariate ROC analysis assessed the predictive power of many parameters.

Results:

The demographic characteristics, baseline clinical data, & echocardiographic findings (Table 1).

Table 1 shows that the mean E/A was (1.4 ± 0.6) with range of (0.8 – 3.3), the mean EDT was (175.3 ± 19.7) ms, the mean E/e` Average, was (15.9 ± 4.4) with range of (9.3 – 26.3), the mean TR V was (3.1 ± 0.2) with range of (2.8 – 3.6) m/s & the mean PASP was (47.1 ± 6.7) mmHg with range of (39 – 65) in all studied patients. Regarding LAVI, the mean was (44.3 ± 6.8)ml/m2 with range of (35.1 – 59.3), the mean LA V. max was (86.4 ± 16.4) ml, the mean LA V. min was (43.7 ± 12) ml, the mean LA emptying Volume was (42.8 ± 9.5)ml, & the mean LA EF (49.8 ± 7.9)% with range of (34.3 – 63.1) in all studied patients

In table 2 the mean cPA lat. was (98.4 ± 20.5) with range of (45.4 – 139.1), cPA Med. the mean was (62.3 ± 15.9) with range of (38 – 101.6) and, cLA-EMD. the mean was (36 ± 16.1) with range of (4.5 – 74) in all studied patients.

Table 1: Baseline demographic characteristics in all patients studied		
Variable		Value
Age (years)		67.7 ± 5.8
Sex	Males	14 (35.0%)
	Females	26 (65.0%)
BSA (m²)		1.9 ± 0.1
BMI (kg/m²)		32.6 ± 2.8
H2FPEF Score		6 ± 0.7
Paroxysmal AF		4 (10.0%)
HTN		40 (100.0%)
DM		20 (50.0%)
CKD		9 (22.5%)
CVD		28 (70.0%)
Nt-proBNP (pg/ml)		392.2 ± 182.2
General ECHO data		
EF (%)		61.1 ± 4.3
E/A		1.4 ± 0.6
EDT (ms)		175.3 ± 19.7
E/e` med.		17.4 ± 4.7
E/e` lat.		14.3 ± 4.3
E/e` Ave		15.9 ± 4.4
TR V (m/s)		3.1 ± 0.2
PASP (mmHg)		47.1 ± 6.7
LAVI (ml/m²)		44.3 ± 6.8
LA V. max (ml)		86.4 ± 16.4
LA V. min (ml)		43.7 ± 12
LA emptying Volume (ml)		42.8 ± 9.5
LA EF %		49.8 ± 7.9

Values are shown as mean ± SD or frequency (%). BMI: Body mass index, BSA: Body surface area,EF: LV ejection fraction using 2-D assessment, E/A: Early to Late Diastolic Transmitral Velocity Ratio, EDT: E-wave Deceleration Time, E/e` med: Early Mitral Inflow Velocity to Early Diastolic medial Mitral Annular Velocity E/e` Lat : Early Mitral Inflow Velocity to Early Diastolic lateral Mitral Annular Velocity, E/e` Ave: Average of E/e` med & E/e` lat, TRV: Tricuspid Regurgitation Velocity, PASP: Pulmonary Artery Systolic Pressure, LAVI: LA Volume Index, LA V. max: Maximum LA Volume, LA V.min: Minimum LA Volume. LA EF: LA Emptying Fraction.

Table 2: Description of LA-EMD by tissue doppler in all studied patients	
Electromechanical delay	(n= 40)
cPA lat. (ms)	98.4 ± 20.5
cPA Med. (ms)	62.3 ± 15.9
cLA-EMD. (ms)	36 ± 16.1

Values are shown as mean ± SD or frequency (%). cLA-EMD: Corrected Left Atrial Electromechanical Delay PA: Time interval from onset of P wave to the late diastolic wave cPA lat: Corrected PA Lateral cPA Med: Corrected PA Medial.

In Table 3, NT-proBNP levels did not correlate with left atrial (LA) electromechanical delay (EMD), volumes, or functional characteristics (P > 0.05) in the study group. Significant positive relationships were seen between NT-proBNP and diastolic dysfunction measures, including E/A ratio (r = 0.478, P = 0.002), E/e′ medial (r = 0.912, P < 0.001), E/e′ lateral (r = 0.876, P < 0.001), and average E/e′ (r = 0.915, P < 0.001). NT-proBNP was positively linked with TRV (r = 0.478, P = 0.002) and PASP (r = 0.478, P = 0.00 Additionally, cLA-EMD was favorably linked with TRV (r = 0.387, P = 0.014) and PASP (r = 0.435, P = 0.005).

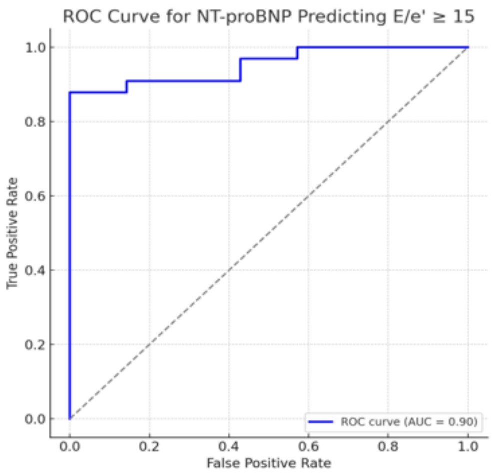
Corrected PA-medial (cPA-MED) showed a high inverse connection with BMI (r = –0.582, P < 0.001) and a substantial positive correlation with PA-lateral (r = 0.634, P < 0.001). cPA-MED was positively linked with LA volume index (LAVI; r = 0.352, P = 0.026) and minimal LA volume (LAVmin; r = 0.317, P = 0.046).

These findings show that NT-proBNP is more strongly correlated with diastolic dysfunction and pulmonary pressures than LA anatomy or conduction characteristics. NT-proBNP and E-wave deceleration time inversely correlated (r = –0.313, P = 0.049).

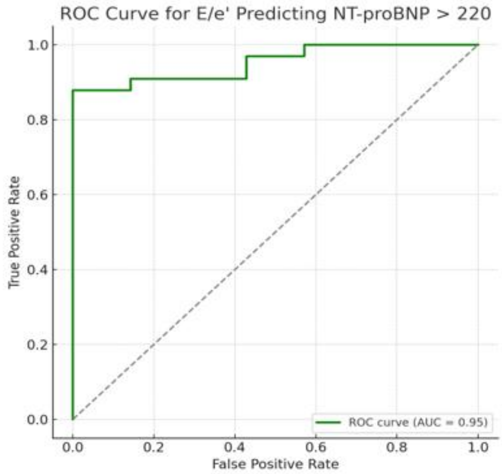
Table 3: Correlations between (Nt-proBNp & CLA-EMD) & all echocardiographic parameters in all studied patients

Parameter	R	P
Nt-proBNp		
EF	-0.038	0.817
E/A	0.478	0.002 **
EDT	-0.313	0.049 *
E/e′ (medial)	0.912	<0.001 **
E/e′ (lateral)	0.876	<0.001 **
E/e′ (average)	0.915	<0.001 **
TR V	0.477	0.002 **
PASP	0.444	0.004 **
LAVI	0.234	0.146
LA V max	0.181	0.262
LA V min	0.183	0.257
LA emptying volume	0.082	0.615
LA EF	-0.045	0.783
cPA lateral	0.147	0.366
cPA medial	-0.095	0.559
cLA-EMD	0.281	0.079
CLA-EMD		
EF	-0.142	0.382
E/A	0.012	0.941
EDT	-0.214	0.186
E/e’ med	0.209	0.196
E/e` lat.	0.165	0.309
E/e` Av	0.192	0.235
TR V	0.387	0.014
PASP	0.435	0.005
LAVI	0.066	0.686
LA V max	0.07	0.670
LA V min	0.242	0.133
La emptying V	-0.185	0.254
LA EF	-0.31	0.051

Following ACC and HFA-PEFF diagnostic criteria for HFpEF, ROC curve analysis was conducted to assess the connection between E/e′ ratio and NT-proBNP levels. There were two main analyses: NT-proBNP predicts E/e′ ≥ 15 with an AUC of 0.90 and an ideal cut-off value of 402 pg/mL (sensitivity: 72.2%, specificity: 90.9%); E/e′ predicts NT-proBNP > 220 pg/mL with an AUC of 0.95 and an optimal cut-off value of 12.62 (sensitivity: 87.88%, specificity: 100%). These results show outstanding discriminatory power and confirm E/e′ and NT-proBNP's reciprocal predictive value in HFpEF evaluation. Figure 3



(A)



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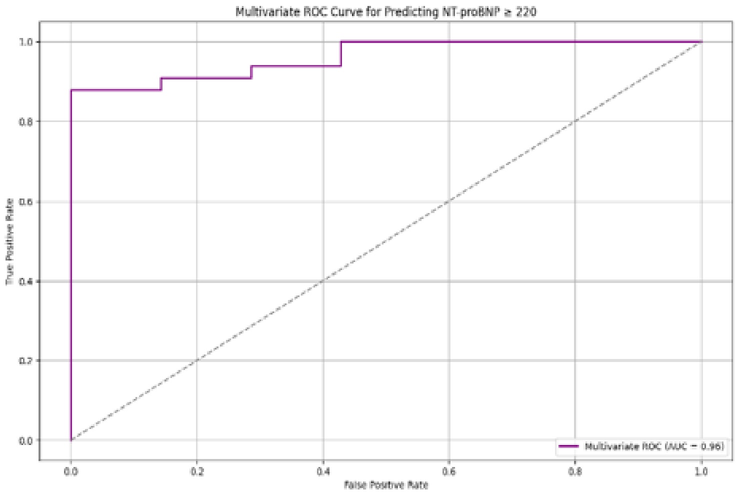

(c)

Figure 3: ROC Analysis (A): NT-proBNP Predicting E/e' ≥ 15, (B) E/e' Predicting NT-proBNP ≥ 220 & (C) Multivariate Model ROC Analysis for predicting NT-pro BNP ≥ 220 pg/ml

The E/e' ave parameter individually shows strong predictive ability with an AUC of 0.95 & high sensitivity. The cumulative multivariate logistic regression model provides excellent prediction capability for NT-proBNP levels ≥ 220 with sensetivity 89% AUC of 0.96. **Table 4**

Table 4: Multivariate Model ROC Analysis

	AUC	Sensitivity	Specificity
E/A + EDT	0.81	83%	72%
E/A + E/e Av	0.87	88%	78%
All Variables Combined	0.96	89%	85%

A significant inversely relationship was noticed between cPA-lat. & BMI (P= 0.001) (r= 0.525), & LA EF (P= 0.013) (r= -0.389) in all studied patients. A statistically significant positive relationship was identified between cPA-lat. & TRV (P= 0.009) (r= 0.408), LA V min (P= 0.005) (r= 0.436), & LAVI (P= 0.041) (r=0.324) in all studied individuals. No significant (P>0.05) correlation between cLA-lat. & other mentioned parameters in all studied patients. Table 5

Table 5: Correlation analysis between cPA-lat & other studied parameters was performed in all patients.		
	CPA Lat	
	r	P-value
BMI	-0.525	0.001
EF	-0.339	0.032
E/A	0.166	0.306
EDT	-0.161	0.321
E/e' med	0.027	0.868
E/e` lat.	0.035	0.828
E/e` Av	0.032	0.846
TR V	0.408	0.009
EPASP	0.26	0.105
LAVI	0.324	0.041
LA V max	0.278	0.082
LA V min	0.436	0.005
La emptying V	-0.069	0.671
LA EF	-0.389	0.013

Values are showed as mean ± SD or frequency (%). The following abbreviations are used in this study: ***EF:*** *LV ejection fraction assessed by 2-D echocardiography,* ***E/A:*** *Early to late diastolic transmitral velocity ratio,* ***E/e' med:*** *Ratio of early mitral inflow velocity to early diastolic medial mitral annular velocity,* ***E/e' lat:*** *Ratio of early mitral inflow velocity to early diastolic lateral mitral annular velocity,* ***E/e' ave:*** *Average of E/e' med & E/e' lat,* ***TRV:*** *Tricuspid regurgitation velocity,* ***PASP:*** *Pulmonary artery systolic pressure,* ***LAVI:*** *LA volume index,* ***LA V. max:*** *Maximum LA volume,* ***LA V. min:*** *Minimum LA volume,* ***LA EF:*** *LAemptying fraction,* ***cLA-EMD:*** *Corrected left atrial electromechanical delay,* ***PA:*** *Time interval from onset of P wave to the late diastolic wave,* ***cPA lat:*** *Corrected PA lateral,* ***cPA med:*** *Corrected PA medial*

Summary of the results: No significant (P>0.05) correlation between (Nt-proBNp, LA-EMD, & left trial volumes & function) in all studied patients. A notable significant positive association between Nt-proBNp & each of E/A (r= 0.478), E/e' med (r= 0.912), E/e' lat (r= 0.876), E/e' AV (r= 0.915), TRV (r= 0.478), & PASP (r= 0.478). A significant negative correlation (r= -0.313) between Nt-proBNp & EDT in all studied patients. Statistical analysis demonstrated a significant positive association among cLA-EMD & TRV (r= 0.387), & EPASP (r= 0.435) in all patients studied. Analysis demonstrated a strong negative association (r = −0.582, P < 0.001) among cPA-MED & BMI in all studied patients.

Discussion

The geographical prevalence of heart failure (HF) in Egypt ranges from 40.9% in Upper Egypt to 72.5% in Alexandria, making it a common clinical condition, especially among older persons [12–14]. HF was divided into three categories based on the left ventricular ejection fraction (LVEF): HFrEF (<40%), HFmrEF (40–49%), & HFpEF (≥50%).

NT-proBNP levels did not significantly correlate with atrial electromechanical delay (EMD) indices like PA-lateral, PA-septal, or cLA-EMD, nor with left atrial (LA) volume or function parameters like LAVmax, LAVmin, LAEF, & LAVI. These results support earlier studies by Porpaczy et al. [15] & Tuluce et al. [16], suggesting that NT-proBNP might not be a sensitive indicator of atrial electrical remodeling in HFpEF.

Nonetheless, there were notable correlations found between right heart pressure & LA-EMD parameters. Tricuspid regurgitation velocity & pulmonary artery systolic pressure (PASP) were positively connected with cLA-EMD, whereas BMI, EF, LAVI, & LAEF were further correlated with cPA-med & cPA-lat. These results point to a possible connection between pulmonary hypertension or right ventricular load & atrial conduction delay. This was further supported by research by Yildiz et al. [17] & Thenappan et al. [18], which showed that higher PASP & TRV are linked to extended LA-EMD & raised LA pressure. Furthermore, NT-proBNP was shown to have substantial positive relationships with diastolic function indices such as the E/A ratio, E/e′ (medial, lateral, & average), TRV, & PASP. According to Myhre et al. [19], Dirsiene et al. [20], Uraizee et al. [21] & Woods et al. [22], these findings support the notion that NT-proBNP serves as a marker of pulmonary hypertension & ventricular diastolic dysfunction.

Limitations:

This was a single-center study with a relatively small sample size & no healthy control group, which may limit generalizability. LA fibrosis, a known contributor to EMD, was not assessed. Echocardiographic variability & operator dependency may also have influenced the measurements.

Conclusions:

A statistically significant correlation between NT-proBNP levels & left atrial electromechanical delay (including cPA-lat, cPA-med, & cLA-EMD) was not seen in this investigation. Atrial conduction anomalies in HFpEF, however, may be more related to right ventricular overload than to natriuretic peptide increase, since LA-EMD demonstrated better relationships with pulmonary vascular resistance indicators. On the other hand, NT-proBNP demonstrated robust positive associations with tricuspid regurgitation velocity (TRV), pulmonary artery systolic pressure (PASP), & E/e′ ratio, highlighting its usefulness as a biomarker of pulmonary hypertension & left ventricular diastolic dysfunction. With a sensitivity of up to 87%, E/e′ notably showed itself to be a good predictor of NT-proBNP levels in HFpEF; this performance might be further enhanced by combining it with other diastolic function indicators.

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Conflict of Interest: Nil

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