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Obstructive sleep apnea is associated with depressed myocardial mechanoenergetics

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Abstract

Purpose: To evaluate the association between the myocardial mechanoenergetic efficiency index (MEEi) and the Apnea-Hypopnea Index (AHI) in the initial phase of obstructive sleep apnea (OSA) diagnosis.

Methods: In this cohort study, we included a total of 382 eligible participants without cardiovascular disease in a tertiary outpatient clinic between January 2013 and January 2015. We recorded demographic, clinical, polysomnographic and echocardiographic variables of the patients. In addition, myocardial mechanoenergetic efficiency (MEE) and MEEi were calculated by an echocardiography-derived validated measurement.

Results: The mean (±SD) age of the participants was 48.47 ± 12.13, and male/female ratio was 287/95. Comparing with non-OSA, MEEi was significantly lower in OSA patients at all stages (0.35 ± 0.08 vs. 0.42 ± 0.05; $p < .001$). MEEi was negatively correlated with hypertension ($r = -0.518$, $p < .001$), body mass index ($r = -0.382$, $p < .001$), AHI ($r = -0.656$, $p < .001$), total apne ($r = -0.525$, $p < .001$), hypopnea ($r = -0.415$, $p < .001$), systolic pulmonary pressure ($r = -0.318$, $p < .001$), relative wall thickness (RWT; $r = -0.415$, $p < .001$), and positive correlated with left ventricular ejection fraction ($r = 0.586$, $p < .001$). According to multiple linear regression analysis AHI ($\beta = -0.625$, $p < .001$), total apnea ($\beta = -0.402$, $p = .001$), hypopnea ($\beta = -0.395$, $p = .001$), LV ejection fraction ($\beta = 0.478$, $p < .001$) and RWT ($\beta = -0.279$, $p < .001$) have an independent relationship with MEEi.

Conclusions: MEEi was lower in OSA patients. A reduced MEEi may reflect a disturbance in energy use of the myocardium. Consequently, our results may provide insight into the mechanisms leading to structural cardiac diseases in OSA patients.

KEYWORDS

apnea-hypopnea index, myocardial energetics, myocardial mechanoenergetic efficiency index, obstructive sleep apnea

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a syndrome described as recurrent apnea and hypopnea episodes during sleep, resulting in systolic and diastolic cardiac dysfunction.[1,2] Global estimates show that 2%–4% of middle-aged people are affected by OSA.[3] OSA is a recently defined cardiovascular risk factor, and it is also related to other risk factors such as metabolic syndrome, obesity, and hypertension.[4] In the past decade, the prevalence of OSA has increased significantly due to the obesity epidemic.

Cardiac metabolism depends on aerobic oxidation for continuous energy supply, with an association between LV structure, function,

and myocardial oxygen consumption (MVO_2). The term "myocardial mechano-energetic efficiency (MEE)" refers to the LV pump efficiency. And, it is a ratio between external work and MVO_2 at each beat.[5] In healthy individuals, the generated energy consumed for LV contraction is around 25%, and the residual energy is mostly wasted as heat.[6] Therefore, cardiac stroke work and oxidative metabolism could be evaluated with invasive methods or sophisticated processes like scintigraphy and cardiac magnetic resonance imaging (CMR).[7,8] According to the technique, MEE measurement reliability and repeatability could be inconsistent, such as 6.3% variation in CMR and 12.9% variation in echocardiography. This discrepancy is mainly based on stroke volume assessment methods. Echocardiographic calculations were lower than CMR as a result of the underestimation of LV volumes. Although CMR and PET imaging are accepted as the gold standard and accurate, they are not practical and applicable in clinical practice. DeSimone et al proposed a new marker derivated from echocardiography that could predict MEEi. This marker states the volume of blood pumped in one beat in 1sn for each gram of heart muscle.[9]

Recent studies have demonstrated that intermittent hypoxemia and arousals could cause ventricular transmural wall stress in OSA patients and result in left ventricular (LV) hypertrophy and dysfunction.[2] Furthermore, hypoxemic episodes can induce adrenergic activity that causes increased LV afterload and heart rate (HR). The combination of these two conditions can stimulate myocardial oxygen consumption and demand. Therefore, we considered that OSA severity and high apnea-hypopnea index (AHI) might impair the LV's ability to switch chemical energy into mechanical energy. Based on this consideration, we examined the relationship between AHI and MEEi with an echocardiography-based measurement.

2 | METHODS

2.1 | Patients

We conducted a cross-sectional cohort study of 382 consecutive individuals referred to Suleyman Demirel University Hospital Respiratory Medicine Department sleep laboratory to evaluate possible OSA between January 2013 and January 2015. In the first step, 421 subjects were assessed for inclusion.

Patients with heart failure [typical symptoms and signs, depressed LV ejection fraction (EF)]; valvular heart disease (hemodynamically significant regurgitation/stenosis); coronary heart disease (known percutaneous intervention or coronary artery bypass graft surgery history); atrial fibrillation or any arrhythmia; chronic renal and hepatic disease; a history of malignancy; or a suboptimal echo window were excluded from the study. Thirty-nine individuals were excluded based on their poor echocardiographic windows ($n = 3$), clinically significant valvular heart disease ($n = 10$), coronary artery disease ($n = 17$), and atrial fibrillation ($n = 9$) left-over 382 patients (287 males and 95 females). From the remaining 382 participants, 296 patients were grouped as OSA (AHI ≥ 5), and 86 individuals were grouped as non-OSA (AHI < 5). Then, OSA patients were then categorized as mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30) and severe (30 ≤ AHI) according to AHI.

Based on 2007 American Diabetes Association guidelines, patients with plasma glucose >125 mg/dl or taking antidiabetic therapy are defined as diabetes mellitus (DM) (9). Obesity is defined as a body mass index (BMI) of at least 30 kg/m^2. According to American Heart Association/The International Diabetes Federation definition,[10,11] increased waist circumference (≥102 cm in men and ≥88 cm in women), increased fasting triglycerides (≥150 mg/dl), decreased HDL cholesterol (<40 mg/dl in men and <50 mg/dl in women), elevated blood pressures (≥130/85 mmHg) and fasting plasma glucose ≥100 mg/dl are the metabolic syndrome (MetS) criteria. Patients with three or more of the above criteria are defined as MetS.

Blood pressure measurements were recorded using a semiautomatic blood pressure monitor (Omron, M1 Basic) in an echocardiography department after sitting and resting for 5 min. Hypertension (HT) was determined as systolic blood pressure (SBP) above 140 mmHg and diastolic blood pressure (DBP) above 90 mmHg, or participants were under antihypertensive treatments according to guideline.[12] In addition, we have noted medical therapy according to the guideline that could affect the MEE, such as beta-blockers, calcium channel blockers (CKB), diuretics and renin-angiotensin system (RAS) blockers.[12]

2.2 | Polysomnography

Polysomnography (PSG) was performed in a quiet place with stable climate conditions. Data were analyzed with a Compumedics (44-channel E-series, Australia) PSG device. Electroencephalography, 2-channel electrooculography, electromyography, oronasal airflow, thoracoabdominal movements, body position, and pulse oximetry (oxygen saturation measured from the fingertip) were monitored during the procedure. According to the American Sleep Disorders Association criteria, an experienced chest disease specialist scored the PSG results.[13]

Apnea is described as a cessation of the airflow signal for 10 s per hour. Hypopnea is identified as a ≥30% decrease in the airflow signal, associated with cortical arousal or oxygen desaturation of ≥3%. The number of apneas plus hypopnea incidents in 1 hr during sleeping is calculated as the AHI. Patients with an AHI of less than 5 were considered OSA negative. This index was used to stratify OSA severity, as mentioned above.

2.3 | Echocardiography

Echocardiographic examination performed after polysomnography. Patients were located in the left lateral decubitus position during the procedure using a Philips iE33 Echocardiography machine with a 2.5 MHz transducer. One experienced cardiologist performed the examinations. Standard two-dimensional echocardiography, M-mode, and Doppler methods were obtained from the apical and parasternal

windows according to the American Society of Echocardiography recommendations. The related parameters were calculated according to the guidelines (14–21).

Transmitral flow velocities were recorded with PW Doppler by positioning sample volume at the level of mitral leaflet tips in the apical four-chamber view. The peak early (E) wave velocity, peak late (A) wave velocity and the mitral deceleration time (DecT) were measured.[14,15] Tissue Doppler imaging recordings were acquired from both the medial and lateral mitral annulus. Myocardial peak early (*E*′) and late (*A*′) diastolic velocities were recorded and averaged; the ratios *E*'/A' and *E*/*E*' were also calculated.[15] The modified Bernoulli equation is used to calculate systolic transtricuspid pressure gradient using peak TR velocity. Systolic pulmonary artery pressure (sPAP) was derived from the addition of right atrial pressure, which was assumed by the quantitative assessment of inferior vena cava, to systolic transtricuspid pressure gradient.[16]

Echocardiographic stroke volume (SV) was calculated as the difference between LV end-diastolic and end-systolic volumes by biplane Simpsons method. External myocardial work, which may be expressed as stroke work (SW), is calculated from SBP times SV and converted in gram-meters by multiplying with 0.0144.[9,17–20] The MVO_2 is calculated as SBP times HR. For this reason, MEE can be expressed as the optimal amount of blood pumped in 1 s with a heartbeat. Thus, MEE can be formulated as:

$$\mathrm{MEE} = \frac{\mathrm{SW}}{\mathrm{MVO2}} = \frac{\mathrm{SBP\,x\,SV}}{\mathrm{SBP\,x\,HR}} = \frac{\mathrm{SV}}{\mathrm{HR}}$$

MEEi estimates the optimal amount of blood pumped with each gram of LV mass in 1 s. It can be calculated as MEE divided by LVM[9,19] and formulated below:

$$\mathrm{MEEi} = \frac{\mathrm{MEE}}{\mathrm{LVM}}$$

2.4 | Statistical analysis

We performed statistical analyses using SPSS version 22.0 (IBM Corp., Chicago, Illinois). Kolmogorov–Smirnov and Shapiro–Wilk tests were

TABLE 1 Demographic, clinical variables of the study population

	Non-OSA ($n = 86$)	Mild OSA ($n = 82$)	Moderate OSA ($n = 94$)	Severe OSA ($n = 120$)	*p*-Value[a]
Age (year)	44.93 ± 11.24	46.22 ± 11.32	49.49 ± 10.27	51.38 ± 11.33	<0.001
Sex (M/F)	60/26	60/22	70/24	97/23	0.308
Smoking (%)	37 (43)	34 (41.5)	25 (26.6)	38 (31.7)	0.059
DM (%)	12 (14)	20 (24.4)	24 (25.5)	47 (39.2)†,‡,**	0.001
HT (%)	15(17.4)	20 (24.4)	37 (39.4)	59 (49.2) †	<0.001
Obesity (%)	13 (15.1)	20 (24.4)	26 (27.7)	54 (45)	<0.001
MetS (%)	13 (15.1)	23 (28)	36 (38.3)	65 (54.2) †,‡,**	<0.001
BMI (kg/m^2)	27.62 ± 3.02	29.34 ± 4.99	30.74 ± 6.53	32.41 ± 5.23	<0.001
Waist Circumference (cm)	94.09 ± 18.37	96.85 ± 18.73	99.36 ± 20.45	104.34 ± 16.42	0.002
HR (beat per min)	72.74 ± 7.30	71.45 ± 8.03	73.33 ± 8.26	86.38 ± 12.57†,‡,**	<0.001
SBP (mmHg)	124.29 ± 7.63	125.08 ± 8.09	128.03 ± 8.73	128.79 ± 8.78†,‡	<0.001
DBP (mmHg)	81.63 ± 3.62	83.27 ± 5.35	83.65 ± 5.36	84.15 ± 5.67†	0.005
AHI	1.65 ± 1.85	10.76 ± 2.72†,**	24.11 ± 4.26†,‡	58.75 ± 19.52†,‡,**	<0.001
Total apnea	0.36 ± 0.77	2.66 ± 2.35**	8.87 ± 6.47†,‡	36.34 ± 25.68†,‡,**	<0.001
Hypopnea	1.28 ± 1.55	8.19 ± 3.00†,**	16.24 ± 7.50†,‡	22.53 ± 13.44†,‡,**	<0.001
Central apnea	0.16 ± 0.66	0.55 ± 0.89	0.87 ± 1.33	1.78 ± 3.05†,‡,**	<0.001
Arousal ındex	12.14 ± 16.45	16.47 ± 14.33	18.41 ± 16.72	24.28 ± 20.07†,‡	0.001
Beta-blockers	7 (9.1)	10 (12.8)	11 (13.6)	26 (17.8)	0.338
Ca^{+2}- Ch. blockers	8 (10.4)	14 (17.9)	16 (19.8)	31 (21.2)	0.242
Anti-RAS	12 (13.5)	27 (32.9)†	37 (39.3)†	59 (49.1)†	<0.001
Diuretics	10 (13)	13 (16.7)	13 (16)	57 (39) †,‡,**	<0.001

Note: Data are expressed as number (%) or mean ± SD. Post hoc comparisons were made with Tukey and Mann–Whitney *U* test and evaluated with Bonferroni correction. †Compared with non-OSA group, $p < .05$. ‡Compared with mild OSA group, $p < .05$. **Compared with moderate OSA group, $p < .05$.

Abbreviations: AHI, Apnea-hypopnea index; BMI, Body mass index; Ca + 2- Ch. Blockers, Calcium channel blockers; DBP, Diastolic blood pressure; DM, Diabetes mellitus; HR, Heart rate; HT, Hypertension; M/F, Men/Female; MetS, Metabolic syndrome; OSA, Obstructive sleep apnea; RAS, Renin-angiotensin system; SBP, Systolic blood pressure.

[a]Tested with one way ANOVA and chi-square.

used to determine the data suitability for normal distribution. Numerical variables with normal distribution were presented as mean ± standard deviation and categorical variables as percentages (%). Subgroup comparison tests were performed using the chi-square test for categorical variables and the Kruskal–Wallis and one-way ANOVA tests for continuous variables. Post hoc comparisons were made with Tukey and Mann–Whitney *U* test and evaluated with Bonferroni correction.

Correlation analyses between MEEi and various echocardiographic and clinical parameters were done using the Pearson or Spearman test for categorical variables. Those results with significant correlations were taken into multiple linear regression analysis to determine the independent predictors of MEEi. The variables (AHI, total apnea, hypopnea, central apnea, age, obesity, HT, DM, MetS, BMI, waist circumference, beta-blockers, CCB, diuretics, RAS blockers, SBP, DBP, LV EF, RWT, *E* wave, *A* wave, DecT, *E*/*A*, *E*/*E*' ratio) found $p < .05$ were considered in an ordered multiple linear regression model. All statistical tests were two-tailed. A *p*-value of less than .05 was considered to show statistically significant results.

2.5 | Ethical considerations

We conducted the study under the Declaration of Helsinki. The Ethical Committee approved the study for Clinical Studies of Suleyman Demirel University School of Medicine (Registration Number: 181). All patients were informed about the study procedure and gave consent to participate in the study.

3 | RESULTS

The results of demographic, clinical variables between the control and OSA groups are summarized in Table 1. Among the 382 participants, 75.1% (287) were males. The mean age was 48.47 ± 12.13 years. Participants were predominantly middle-aged, obese and less often female. Patients with OSA were older, more often diabetic, more often hypertensive and had higher BMI values than those without OSA. All OSA patients were in the early phase of diagnosis. Moreover, almost one-third of the OSA population was in the severe OSA group.

Table 2 shows the echocardiographic parameters of the study subgroups. LV internal dimensions, sPAP, RWT, LVM, and LVM index tend to increase with OSA severity. However, the Mitral E wave and E/A ratio were reduced in patients with OSA compared with non-OSA. In Figure 1, there is a clear trend of decreasing MEEi from non-OSA to severe OSA. Mean MEEi was 0.62 ± 0.17 in total study group, and comparing with non-OSA, MEEi was significantly lower in OSA patients at all stages. (0.75 ± 0.14 vs. 0.58 ± 0.16; $p < .001$).

Further, we performed univariate analysis to specify the echocardiographic and clinical changes associated with myocardial MEEi

TABLE 2 2D, M-mode and Doppler echocardiographic measurements of the study population

	Non-OSA ($n = 86$)	Mild OSA ($n = 82$)	Moderate OSA ($n = 94$)	Severe OSA ($n = 120$)	*p*-Value[a]
IVS (mm)	10.09 ± 0.76	10.40 ± 0.95†	10.78 ± 1.22†,‡	11.52 ± 1.44†,‡,**	<0.001
PW (mm)	9.02 ± 0.67	9.62 ± 0.85†	10.10 ± 0.96†,‡	10.60 ± 1.19†,‡,**	<0.001
LVDd (mm)	48.91 ± 2.77	49.15 ± 2.65	50.03 ± 3.86†	50.46 ± 3.34†,‡	0.002
LVSd (mm)	27.06 ± 2.31	27.62 ± 2.27	28.17 ± 3.03†	29.26 ± 3.25†,‡	<0.001
LA (mm)	36.78 ± 3.74	37.51 ± 2.83†	38.44 ± 3.43†,‡	40.37 ± 3.41†,‡,**	<0.001
LV EF (%)	65.24 ± 3.59	64.07 ± 3.49	63.60 ± 4.27†	61.62 ± 5.25†,‡	<0.001
RWT	0.391 ± 0.025	0.407 ± 0.036†	0.420 ± 0.047†,‡	0.440 ± 0.049‡,**	<0.001
LVM	169.58 ± 26.48	181.47 ± 30.73†	198.44 ± 39.98†,‡	219.03 ± 47.93†,‡,**	<0.001
LVMi	88.32 ± 13.07	93.47 ± 16.92	100.17 ± 20.29†	106.73 ± 23.76†,‡	<0.001
SV	89.80 ± 7.12	87.29 ± 8.41	85.38 ± 8.26**	84.58 ± 9.20**	<0.001
SW	148.52 ± 20.32	149.10 ± 19.05	158.45 ± 22.74†	159.09 ± 28.40†,‡	0.001
MVO_2	8945 ± 1232	9050 ± 1150†	9409 ± 1302†,‡	10 211 ± 1779†,‡,**	<0.001
DecT (msn)	177.96 ± 31.19	185.38 ± 40.38	190.05 ± 39.96†	226.15 ± 37.08†,‡,**	<0.001
E/A ratio	1.18 ± 0.12	1.01 ± 0.14†	0.86 ± 0.14†,‡	0.78 ± 0.12†,‡,**	<0.001
E/E' ratio	9.32 ± 1.35	10.06 ± 1.63	10.48 ± 1.60†	11.85 ± 1.81†,‡	<0.001
sPAP(mmHg)	27.76 ± 5.59	31.94 ± 7.37†	32.70 ± 5.91†,‡	35.69 ± 5.71†,‡,**	<0.001

Note: Data are expressed as number (%) or mean ± SD. Post hoc comparisons were made with Tukey and Mann–Whitney *U* test and evaluated with Bonferroni correction. †Compared with non-OSA group, $p < .05$. ‡Compared with mild OSA group, $p < .05$. **Compared with moderate OSA group, $p < .05$.

Abbreviations: DecT, Deceleration time; IVRT, Isovolumic relaxation time; IVS, Interventricular septum; LV EF, Left ventricular ejection fraction; LV, Left ventricular; LVDd, Left ventricular diastolic dimension; LVM, Left ventricular mass; LVMi, Left ventricular mass index; LVSd, Left ventricular systolic dimension; MEEi, Myocardial mechanoenergetic efficiency index; MVO_2, Myocardial energy consumption; OSA, Obstructive sleep apnea; PW, Posterior wall; RWT, Relative wall thickness; sPAP, Systolic pulmonary pressure; SV, Stroke volume; SW, Stroke work.

[a]Tested with one way ANOVA and Kruskal–Wallis.

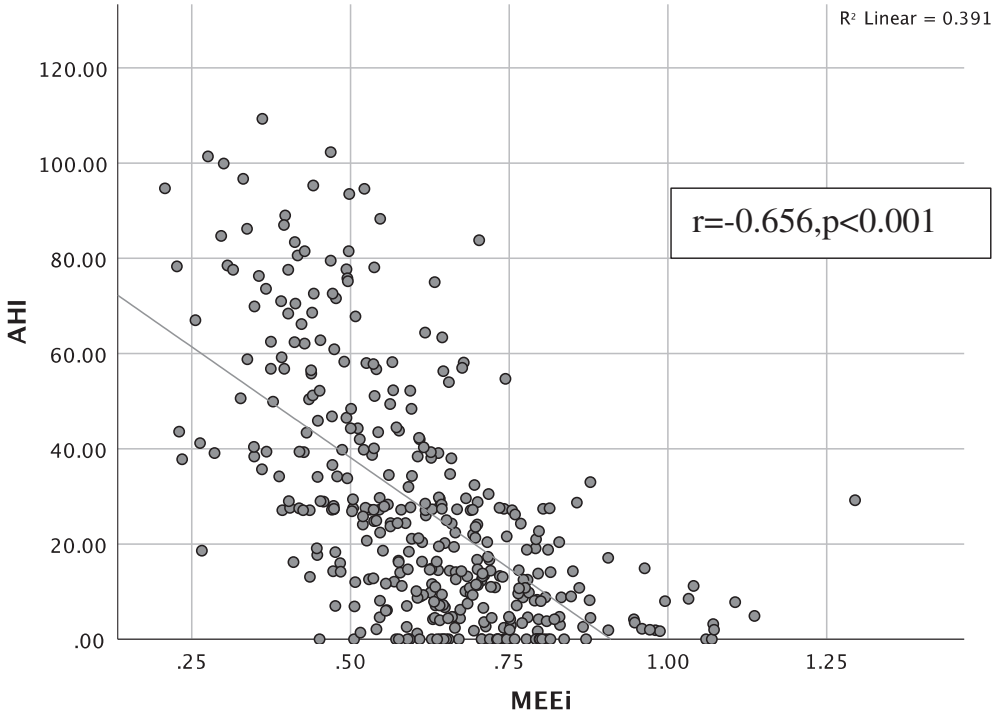

FIGURE 1 Correlation between myocardial mechanoenergetic efficiency index and apnea-hypopnea index. AHI, apnea-hypopnea index; MEEi, myocardial mechanoenergetic efficiency index

TABLE 3 Univariate and multiple linear regression analysis of MEEi with clinical and echocardiographic measurements

	r	*p*-Value	*β*	*p*-Value
Age	−0.208	<0.001	-	-
HT	−0.518*	<0.001	-	-
BMI	−0.382	<0.001	-	-
Waist circumference	−0.210	<0.001	-	-
SBP	−0.215	<0.001	-	-
Beta-blockers	0.125*	0.010	-	-
Ca^{+2}- Ch. blockers	−0.138*	0.005	-	-
Anti-RAS	−0.143*	0.007	-	-
Diuretics	−0.230*	0.001	-	-
AHI	−0.656	<0.001	−0.625	<0.001
TotApne	−0.515	<0.001	−0.402	0.001
Hypopnea	−0.415	<0.001	−0.395	0.001
LV EF	0.586	<0.001	0.478	<0.001
RWT	−0.415	<0.001	−0.279	<0.001
E/*A*	0.339	<0.001	-	-
E/*E*'	−0.247	<0.001	-	-
DecT	−0.248	0.007	-	-
sPAP	−0.318	<0.001	-	-

Abbreviations: *, Spearmen coefficient; BMI, Body mass index; Ca + 2-Ch. Blockers, Calcium channel blockers; CenApne, Central Apnea; DecT, Deceleration time; HT, Hypertension; LV EF, Left ventricular ejection fraction; MEEi, Myocardial mechanoenergetic efficiency index; r, Correlation coefficient; RAS, Renin-angiotensin system AHI, Apnea-hypopnea index; RWT, Relative wall thickness; SBP, Systolic blood pressure; sPAP, Systolic pulmonary pressure; TotApne, Total Apnea; β, Standardized coefficient β.

(Table 3). All patients in the study, MEEi was inversely related to hypertension ($r = -0.518$, $p < .001$), BMI ($r = -0.382$, $p < .001$), AHI ($r = -0.656$, $p < .001$), Total apnea ($r = -0.525$, $p < .001$), Hypopnea ($r = -0.415$, $p < .001$) sPAP ($r = -0.318$, $p < .001$), RWT ($r = -0.415$, $p < .001$), and positively related with LV EF ($r = 0.586$, $p < .001$). Notably, among all parameters, MEEi showed the strongest negative correlation with AHI ($r = -0.656$, $p < .001$; Figure 1). Next, we used multiple linear regression analysis to predict the independent contribution of MEEi, to differentiate MEEi from AHI, total apnea, hypopnea, LV EF, and RWT. These variables statistically significantly predicted MEEi ($F = 74.513$, $p < .001$, $R^2 = 0.728$). Our model explained 85.6% of the variance of MEEi ($p < .001$; Table 3).

4 | DISCUSSION

The primary objective of our study was to assess the effect of OSA on MEEi. Echocardiographic MEEi calculation grounds on SV, HR and LVM index parameters.[5,19,21] We found that LV dimensions, HR and LVM were the highest in patients with severe OSA. Furthermore, HR, BMI, waist circumference, and SBP were elevated toward OSA severity, and LV conventional diastolic parameters were impaired in all-OSA groups.

Cardiovascular diseases (CVD) and OSA are commonly aggregated because of shared risk factors like obesity, HT and MetS.[22] Before the overt CVD development, earlier observations showed an increase in SBP,[23] LVM and LVM index cause poor prognosis[24] regardless of obesity.[25] Our results were in accordance with the literature. The general mechanisms are high sympathetic activation and oxidative stress, graded as intermediate endpoints before apparent CVD.[22]

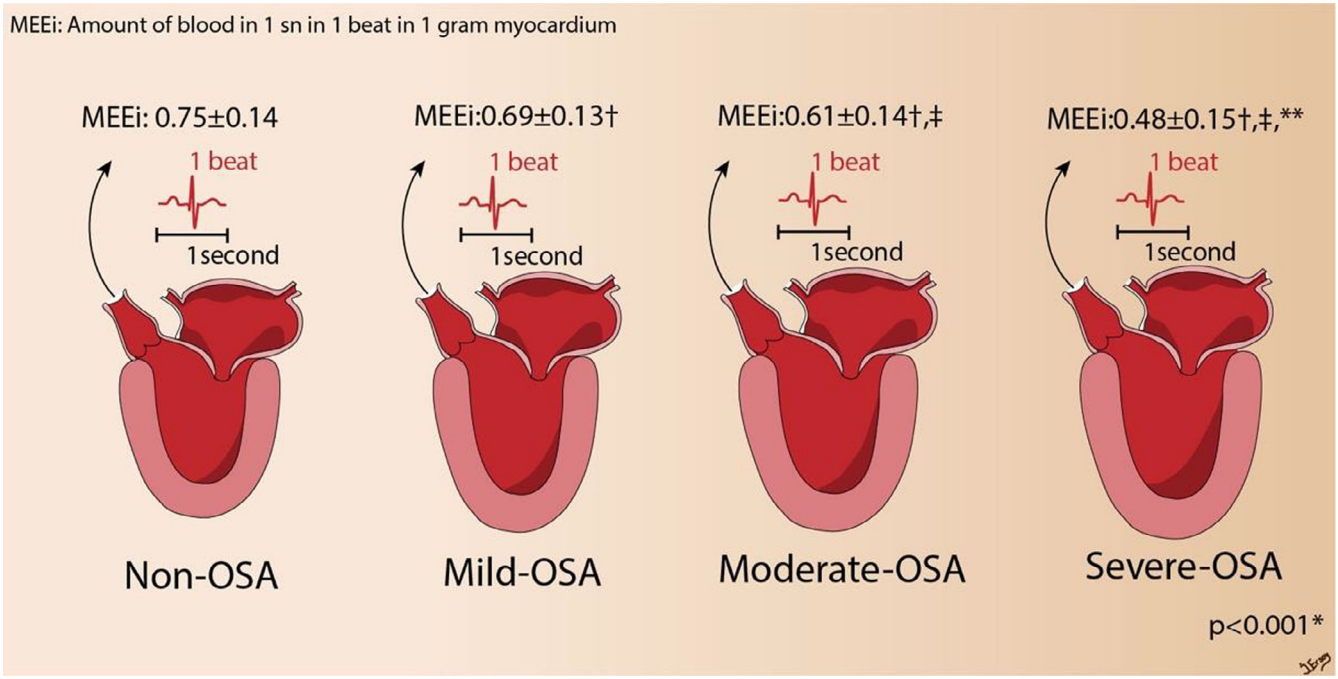

FIGURE 2 An illustration is showing myocardial mechanoenergetic efficiency index patterns changing non-OSA to severe OSA. Data are expressed as mean ± standard deviation. * = Tested with One way ANOVA and Kruskal–Wallis, post hoc comparisons made with Tukey and Mann–Whitney *U* test and evaluated with Bonferroni correction. †Compared with non-OSA group, $p < .05$; ‡Compared with mild OSA group, $p < .05$; **compared with moderate OSA group, $p < .05$. MEEi, myocardial mechanoenergetic efficiency index; OSA, obstructive sleep apnea; sn, second

To the best of our knowledge, we present the first study evaluating myocardial mechanoenergetics in patients with OSA. Our results confirm that LV energetic efficiency depressed with OSA severity (Figure 2). MEEi is a thought-provoking recent marker representing the amount of blood that 1 g of heart muscle can pump in 1 s. Moreover, MEEi integrated three established outcome predictors, such as increased HR, decreased SV and higher LVM, into a single index. Consequently, MEEi is a stronger predictor for heart failure than conventional markers like LVM, HR and SV.[21,26] LV mechanical efficiency is expected to increase with excessive LV mass.[19,20,27,28] Contrary to expectations, we found depressed MEEi with excessive LVM in our OSA study group. As mentioned above, OSA is frequently associated with LV hypertrophy and diastolic dysfunction.[2]

Therefore, we suppose that two underlying mechanisms may explain this: first, the energy loss of the degenerated elastic elements of the left ventricle in OSA,[2] and second, increased myocardial oxygen demand as a result of increased HR and insulin resistance due to increased sympathetic activity caused by intermittent episodes of apnea-hypopnea.[29] Furthermore, insulin resistance inhibits the use of glucose and lactate as energy sources and facilitates the use of free fatty acids. This may cause significantly increased myocardial oxygen consumption that can be considered as workload. Thus, the MEE will decrease, and oxidative stress will increase.

Furthermore, another mechanism for depressed MEEi in OSA may be melatonin deficiency. Some studies showed ventricular wall contains melatonin receptors.[30,31] Melatonin has antifibrotic and antioxidant effects on the myocardium[32] by preventing the Type 1 collagen collection and increasing fibrotic markers such as transforming growth factor- β.[33,34] Repetitive hypopnea and apnea episodes reduce melatonin levels during sleep. Low melatonin could result in cardiac remodeling. Cardiac remodeling and fibrosis may impair the ability of the myocardium to convert adenosine triphosphate to mechanical work.

Several studies showed that MEEi depressed in HT,[9,19] DM,[27] MetS,[26,27,35] primary aldosteronism,[20] non-alcoholic fatty liver disease,[28] and inflammatory arthritis.[5] The studies mentioned show that the mechanisms underlying the decline in MEEi are impaired fat oxidation, adrenergic activation, and pathological LV hypertrophy.[9,19,20,27,28,35] OSA has a causative link between hypertension, metabolic syndrome, and obesity with similar pathologic mechanisms.[29] Furthermore, some critical medications for HT like beta-blockers and RAS blockers could increase MEEi. Catheter-based studies assessing myocardial efficiency showed that beta-blockers and RAS blockers reduced LV afterload and MVO_2 without changing SV.[8,36] Most of the hypertensive patients in our research were taking RAS blockers and diuretics. At the same time, beta-blockers and CKB did not differ among the OSA subgroups (Table 1). These results are in agreement with those obtained by DeSimone et al in hypertensive individuals.[19] However, according to our results, mentioned medications were not an independent contributor of MEEi.

Although the study has a relatively small sample size according to the literature evaluating MEEi, a decrease in MEEi is striking. This result may be due to high AHI that could have an additional negative effect on MEEi. High negative intrathoracic pressure produces augmented LV afterload by increasing the gradient between intracavitary

and extracavitary LV pressures. Moreover, enhanced venous return and pulmonary vasoconstriction due to the hypoxia increase RV afterload. Both mechanisms can cause a decrease in cardiac output. In addition, frequent apneic attacks provoke sympathetic activity. High adrenergic activity may result in HR elevation with increased oxygen consumption. These changes prompt a progressive decrease in MEEi.

We found that parameters we use to assess diastolic functions changes with OSA progression based on the decrease in *E* and *E/A* ratio and increase in IVRT, *E/E'* ratio and DecT. These findings also accord with our earlier observations.[2,37] Our results can be explained by the severe negative intrathoracic pressure resulting in high LV transmural pressure. Moreover, compensatory changes may occur against the increase in LV afterload and cause diastolic dysfunction.

Moreover, we found that RWT was a strong independent predictor for depressed MEEi. The heterogeneous nature of our sample may explain this result as a high proportion of hypertension and obesity. Thus, we cannot rule out the impact of overlapping stated pathologies' with OSA on LV geometry that consequences exaggerated RWT elevation. Our results are in agreement with Mancusi et al's findings which showed hypertension and metabolic syndrome associated with high RWT.[27]

This work suffers from numerous limitations. First, we measured MEE by indirect methods rather than more accurate procedures such as catheter-based measurement or cardiac PET, which are invasive, time-consuming, and expensive and, therefore, not feasible in clinical practice. Scintigraphy is the gold standard in evaluating MEE and is not affordable on a large scale. Second, the study has a cross-sectional design, so we cannot establish a specific causal link between OSA and the depressed myocardial mechanoenergetic situation. Third, it is a single-center experience, and one cardiologist performed the echocardiography. This situation cannot exclude selection or procedure bias. The fourth and important limitation was that our study population was heterogeneous, consisting of obesity, diabetes, HT and MetS, affecting left atrium dilatation, LV size, hypertrophy, diastolic functions, and pulmonary hypertension. Therefore, we fall into the "which came first?: egg and chicken" dilemma in determining the contribution of mentioned comorbidities versus OSA on MEEi. However, our study population was evaluated in the initial part of the OSA diagnosis. So, our findings could demonstrate mechanism by which OSA causes LV impairment in the early steps before the overt heart failure. Eventually, our results need to be interpreted with caution.

Finally, this study was limited to LV functions but could be extended for the right ventricular function evaluation because of the pulmonary vasculature involvement in the OSA pathologic process. These findings may help us to understand CVD occurrence mechanisms in OSA patients.

5 | CONCLUSION

For the first time, our results demonstrate that reduced MEEi is associated with elevated AHI. Patients with OSA have an increased myocardial oxygen expenditure and a reduced LV energetic efficiency. These findings may lead to further studies to clarify the mechanisms underlying CV events' increased risk in OSA patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTIONS

According to the International Committee of Medical Journal Editors (ICMJE), all authors of this manuscript meet the authorship criteria. In addition, all authors have seen and approved the manuscript being submitted and published.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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