



META-ANALYSIS

The impact of continuous positive airway pressure on cardiac mechanics: Findings from a meta-analysis of echocardiographic studies

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Abstract

Current evidence on the effects of continuous positive airway pressure (CPAP) on cardiac mechanics in patients with obstructive sleep apnea (OSA) is based on a few single studies. The authors investigated this topic through a meta-analysis of speckle tracking echocardiography (STE) studies that provided data on left ventricular (LV) and right ventricular (RV) mechanics as assessed by global longitudinal strain (GLS). The PubMed, OVID-MEDLINE, and Cochrane library databases were systematically analyzed to search English-language review papers published from inception to January 31, 2022. Studies were identified by crossing the following terms: "obstructive sleep apnea", "sleep quality", "sleep disordered breathing", "continuous positive airway pressure therapy", "noninvasive ventilation", "left ventricular hypertrophy", "systolic dysfunction", "global longitudinal strain", "left ventricular mechanics", "right ventricular mechanics", "echocardiography" and "STE echocardiography". The meta-analysis, including a total of 337 patients with OSA from nine studies (follow-up 2–24 months) showed a significant GLS improvement in both LV and RV after CPAP, standard mean difference (SMD) being 0.51 ± 0.08 , CI: 0.36–0.66, $p = .0001$ and 0.28 ± 0.07 , CI: 0.15–0.42, $p = .0001$, respectively. Corresponding SMD values for LV ejection fraction (LVEF) and tricuspid annular plane systolic excursion (TAPSE) were 0.20 ± 0.06 , CI: 0.08–0.33, $p = .001$ and 0.08 ± 0.06 , CI: -0.04/0.20, $p = .21$. Our meta-analysis suggests that: I) CPAP treatment exerts beneficial effects on biventricular function in patients with OSA; II) the assessment of cardiac mechanics by STE should be routinely recommended for monitoring cardiac function in this setting, due to limitations of conventional echocardiography in evaluating biventricular performance.

KEYWORDS

continuous positive airway pressure, left and right ventricular strain, obstructive sleep apnea

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1 | INTRODUCTION

Obstructive sleep apnea (OSA) is asleep-related breathing disorder with impressive worldwide growth in parallel with overweight and obesity; it is associated with an increased risk of non-fatal and fatal cardiovascular events as well as all-cause mortality.¹⁻³ The reduction or complete blockage of airflow due to obstruction of the upper airway structures during sleep, resulting in hypoxemia, hypercapnia, intrathoracic pressure changes, autonomic dysfunction and sleep fragmentation, leads to several cardiovascular functional and structural alterations.^{4,5} They include endothelial dysfunction, inflammation, hypertension, left and right ventricular remodeling leading to impaired systolic and diastolic function, silent myocardial ischemia and arrhythmias; these alterations are synergistically responsible for the increased risk of hospitalization, interventional procedures and cardiovascular mortality in patients with OSA.^{6,7}

Given the unfavorable impact of OSA on quality of life and health in the general population, an enormous effort has been made to develop effective therapies over the past four decades. Numerous options, indeed, are now available for this epidemic breathing disorder. In addition to the standard continuous positive airway pressure (CPAP) proposed for the first time by Sullivan and coworkers in the early 1980s, different CPAP techniques (ie, bi-level, auto-titrating, adaptive servo-ventilation), oral appliances, positional therapy, upper airway surgery, life-style and surgical measures aimed to reduce obesity are now available.^{8,9} CPAP therapy is recommended by the National Institute of Health and Care Excellence (NICE) guidelines as the first-line treatment for moderate or severe OSA as well as for mild OSA when other therapeutic interventions have failed or symptoms severely affect patient's quality of life.¹⁰

Numerous studies have shown that CPAP, by reducing or abolishing nocturnal hypoxic episodes, results in the improvement of hemodynamic (ie, blood pressure, arterial stiffness), hormonal (ie, catecholamines) and cardio-metabolic (ie, metabolic syndrome) parameter, thus favorably influencing the cardiovascular prognosis in this setting.^{11,12}

Although no clear evidence is available that CPAP therapy may improve cardiovascular outcomes, including heart failure (HF) frequently associated to OSA, a mounting body of evidence suggests that this treatment exerts beneficial effects on cardiac function.^{13,14} A meta-analysis of ten controlled trials showed that left ventricular ejection fraction (LVEF) improved significantly after CPAP treatment in patients with HF but not in those without HF.¹⁴ Some inconsistent findings in the literature may be ascribed to the fact that LVEF is not sensitive enough to detect subclinical changes in cardiac function and its variations over time. Recently, advanced ultrasound imaging techniques, in particular 2D and 3D speckle tracking echocardiography (STE), have added new information on this topic by targeting myocardial mechanics via global longitudinal strain (GLS), a more sensitive parameter of systolic dysfunction than LVEF and tricuspid annular plane systolic excursion (TAPSE).¹⁵

Starting from these premises we have performed a meta-analysis aimed at providing an up-dated, comprehensive information on the effect of CPAP on systolic function, as assessed by LV and right ventricular (RV) GLS, in patients with OSA.

2 | METHODS

2.1 | Search and study selection

The present research was performed by following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Pertinent literature was systematically scrutinized to identify all papers addressing myocardial strain (ie, GLS) in OSA, as assessed by 2D-3D STE echocardiography.

The PubMed, OVID-MEDLINE, and Cochrane library databases were systematically analyzed to search English-language review papers published from inception to January 31, 2022.

Studies were identified by using Me-SH terms and crossing the following terms: "obstructive sleep apnea", "sleep quality", "sleep disordered breathing", "continuous positive airway pressure therapy", "noninvasive ventilation", "left ventricular hypertrophy", "systolic dysfunction", "global longitudinal strain", "left ventricular mechanics", "right ventricular mechanics", "echocardiography" and "STE echocardiography".

Checks of the reference lists of selected papers integrated the electronic search. Reviews, editorials, and case reports were excluded from analyses, but examined for potential additional references. Two authors (E.G. and C.C.) assessed retrieved abstracts and full text of these studies to establish eligibility according to inclusion criteria mentioned below. A third reviewer (M.T.) resolved disagreements on study judgments. Data extraction was performed by one reviewer (C.C.) and independently checked by another reviewer (E.G.).

Main inclusion criteria were: (I) English review papers published in peer-reviewed journals; (II) studies providing data on LV and/or RV GLS by STE echocardiography; (III) minimum set of clinical/demographic data; and (IV) duration of follow-up longer than 1 month. Specific exclusion criteria were: (I) studies with less than 10 patients with OSA; (II) studies conducted in children and adolescents (age < 18 years); and (III) studies aimed at assessing the effects of a single CPAP session.

2.2 | Echocardiographic methods

Conventional analysis of cardiac structure and function was performed in all studies according to recommendations of contemporary guidelines. LV and RV myocardial deformation (ie, GLS) was measured offline from 2D or 3D echocardiographic images using a commercial dedicated software; R-R gating was used for LV strain assessment. In all studies, LV and RV endocardium was manually traced and corrected, if necessary, and average longitudinal strain curve was automatically provided by the software.

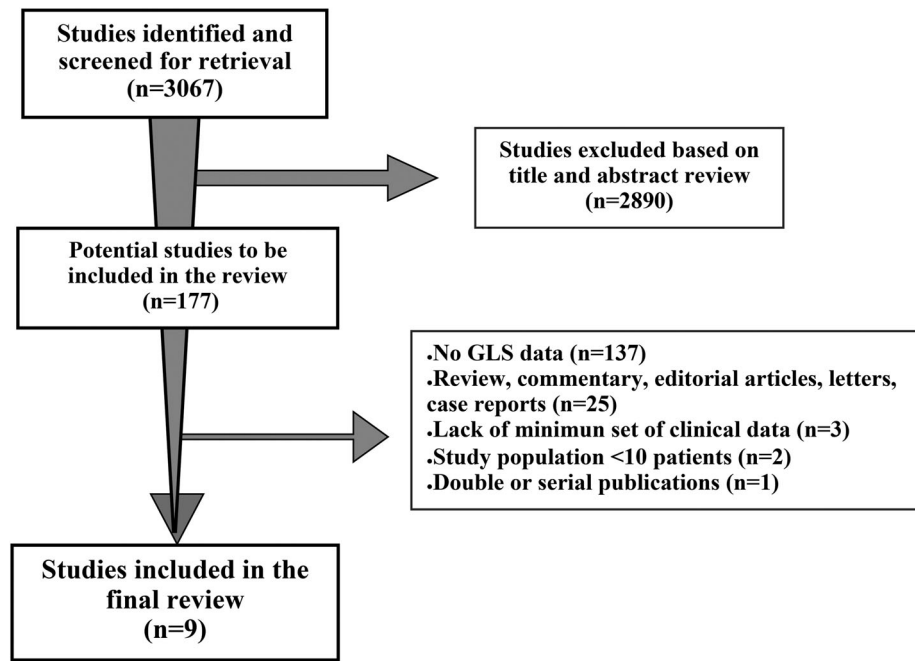


FIGURE 1 Schematic flow-chart for the selection of studies

2.3 | Statistical analysis

The primary outcome of the meta-analysis was to assess the changes in LV and RV GLS induced by treatment with CPAP in patients with OSA. To this purpose, a pooled analysis of cardiac parameters was performed using fixed or random effects meta-analysis by Comprehensive Meta-Analysis Version2, Biostat, Englewood, NJ, USA. Standard means difference (SMD) with 95% confidence interval (CI) was used to calculate the statistical difference of LV and RV GLS, LVEF and TAPSE before and after treatment with CPAP.

Data provided by selected studies are expressed as absolute numbers, percentage, mean \pm standard deviation (SD), mean \pm standard error (SE).

Heterogeneity was estimated by using I-square, Q and tau-square values; random effect models were applied when the heterogeneity across studies was high ($I^2 > 75$) and fixed models when the heterogeneity was lower ($I^2 < 75$). Publication bias was assessed by using the funnel plot according to the trim and fill test. Observed and adjusted values, their lower and upper limits have been calculated. To assess the effect of individual studies on the pooled result, we conducted a sensitivity analysis by excluding each study one by one and recalculating the combined estimates on remaining studies.

3 | RESULTS

The initial literature search identified 3067 papers. After the initial screening of titles and abstracts, 2890 studies were excluded as they were not related to the topic. Therefore, 177 studies were reviewed; of these, 137 did not report data on myocardial mechanics, and 25 were case reports, reviews, commentary, editorial review papers, and

six for miscellaneous reasons. Therefore, a total of nine studies including patients with OSA treated with CPAP for a period longer than one month and containing echocardiographic data of interest, were included in the final review¹⁶⁻²⁴ (Figure 1). The Newcastle-Ottawa Score, used for assessing the quality of the studies, ranged from 7 to 9, the mean score being 7.8.²⁵ Therefore, no study was excluded based on its limited quality.

3.1 | Characteristics of the studies

On the whole 337 patients with OSA were included in nine studies (sample size ranging from 14 to 82 participants), performed in two continental areas (Europe = 6, Asia = 3).

Table 1 shows data regarding the main findings of selected studies such as authors, year of publication, sample size, mean age, sex, body mass index BMI, LV GLS before and after CPAP; CPAP usage and duration, pre- and post-treatment AHI values, clinical setting outcome, STE method. The duration of the follow-up period ranged from 2 to 24 months. Baseline mean AHI values ranged from $35 \pm 15/h$ to $59 \pm 9/h$. The majority of studies included patients without relevant comorbidities and prevalent cardiovascular disease. Four out of nine studies enrolled only patients with severe OSA. OSA was defined according to standard diagnostic criteria.²⁶

3.2 | Echocardiographic findings

3.2.1 | LVEF

LVEF average pooled values were $59.9 \pm 1.6\%$ at baseline and $61.9 \pm 0.9\%$ at follow-up. The meta-analysis revealed a signifi-

TABLE 1 Summary of nine studies targeting the impact of continuous positive airway pressure therapy on myocardial strain in patients with obstructive sleep apnea, as assessed by echocardiography, published from 2010 to 2021

Author (reference)/Year publication	OSA sample size (n)	Age (years)	Sex(% male)	BMI (kg/m ²)	SBP(mm Hg)	LV-GLSpre CPAP (%)	LV-GLSpst CPAP (%)	CPAP usage (h/night)	CPAP duration (months)	Baseline AHI (h)	FinalAHI (h)	Setting	Outcome	STE method
Haruki ¹⁶ 2010	14	na	na	na	na	-18,9±2,2	-20,7±1,6	na	3	56±19	5±8	Moderate to severe OSA without CV disease	LV GLS	2D
Hammersting ¹⁷ 2013	82	63±12	63	31±6	na	na	Na	6,5±1,1	6	31±27	6±7	Mild to severe OSA with prevalent CV disease	RV GLS	2D
Vitarelli ¹⁸ 2013	15	na	na	na	na	-18,3±2,2	-20,2±2,4	6±0,5	4	59±9	4±2	Severe OSA without comorbidities	LV GLS	2D
Vitarelli ¹⁹ 2015	15	na	na	na	na	na	Na	6±0,3	4	58±9	4±2	Severe OSA without comorbidities	RV GLS	3D
D'Andrea ²⁰ 2016	55	68±11	70	34±7	139±8	-11,5±4,1	-14,8±4,5	na	6	35±15	5±8	Mild to severe OSA without CV disease	LV and RV GLS	2D
Vural ²¹ 2017	28	na	na	na	na	-15,5±6,9	-18,8±3,6	5,7±1,2	24	na	na	Mild to severe OSA without pulmonary and CV disease	LV GLS	2D
Kim ²² 2019	26	49±11	92	28±3	na	-17,8±2,1	-20±2,1	4,6±1,2	3	na	na	Severe OSA without CV disease	LV and RV GLS	2D
Chu ²³ 2020	45	na	na	na	na	na	Na	na	24	50±16	5±2	Severe OSA without CV disease	RV GLS	2D
Zota ²⁴ 2021	57	58±9	70	34±6	137±18	-16,1±3,8	-18,6±na	na	2	42±21	na	Moderate to severe OSA with prevalent HTN, DM and obesity	LV GLS	2D

Abbreviations: AHI, apnoea/hypo-apnoea index; BMI, body mass index; SBP, systolic blood pressure; CPAP, = positive airway pressure therapy; DM, diabetes mellitus; GLS, global longitudinal strain; HTN, hypertension; LV, left ventricular; OSA, obstructive sleep apnea; RV, right ventricular; STE, = speckle tracking echocardiography. Data are presented as absolute numbers, percentage, mean ±SD.

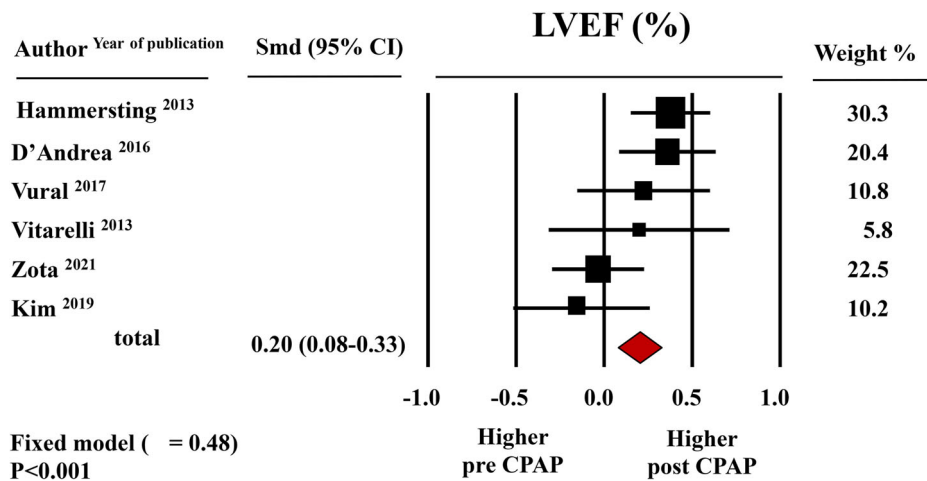


FIGURE 2 Forest plot for standard means difference (SMD) of left ventricular ejection fraction (LVEF) in patients with OSA before and after CPAP (fixed model, $I^2 < 0.75$). Relative weight of each study is reported on the right side. CI = confidence intervals

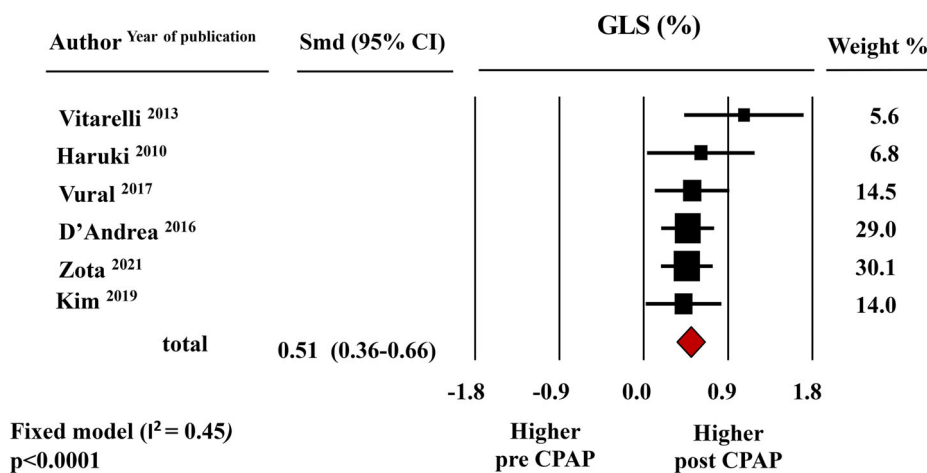


FIGURE 3 Forest plot for standard means difference (SMD) of left ventricular global longitudinal strain (LV GLS) in patients with obstructive sleep apnea (OSA) before and after continuous positive airway pressure (CPAP) treatment (fixed model, $I^2 < 0.75$). Relative weight of each study is reported on the right side. CI = confidence intervals

cant increase in this index of systolic function after CPAP treatment (SMD 0.20 ± 0.06 , CI $0.08/0.33$, $p < .001$) (Figure 2).

no significant changes in this measure of RV longitudinal function after CPAP treatment (SMD 0.08 ± 0.06 , CI $-0.04/0.20$, $p = .21$) (Figure 4).

3.2.2 | LV GLS

Baseline and follow-up mean LV GLS values in the pooled study population (6 studies) ranged from -14.1% to -18.6% and from -16.9% to -20.9%, the average pooled values being $-17.7 \pm 0.6\%$ and $-19.6 \pm 0.4\%$, respectively. Figure 3 depicts the results of the meta-analysis where SMD suggested a significant improvement in LV mechanics after CPAP treatment (0.51 ± 0.08 , CI $0.36/-0.66$, $p < .0001$).

3.2.4 | RV GLS

Pre- and post-treatment mean RV GLS values in the pooled study population (five studies) varied from -15.14% to -20.35% and from -15.9% to -22.6%, the average pooled values being $-17.7 \pm 1.32\%$ and $-19.3 \pm 1.7\%$, respectively. Figure 5 shows the findings of the meta-analysis where SMD suggested an improvement in RV mechanics after CPAP treatment (0.28 ± 0.07 , CI $0.15/0.42$, $p < .0001$).

3.2.3 | TAPSE

Pooled TAPSE values (five studies) were 21.8 ± 1.3 mm at baseline and 21.1 ± 1.2 mm at the end of follow-up. The meta-analysis documented

3.3 | Additional echocardiographic parameters

Pooled left ventricular mass index (three studies) was 106.7 ± 18.2 g/m² at baseline and 104.4 ± 15.1 g/m² at the end of follow-up (SMD -

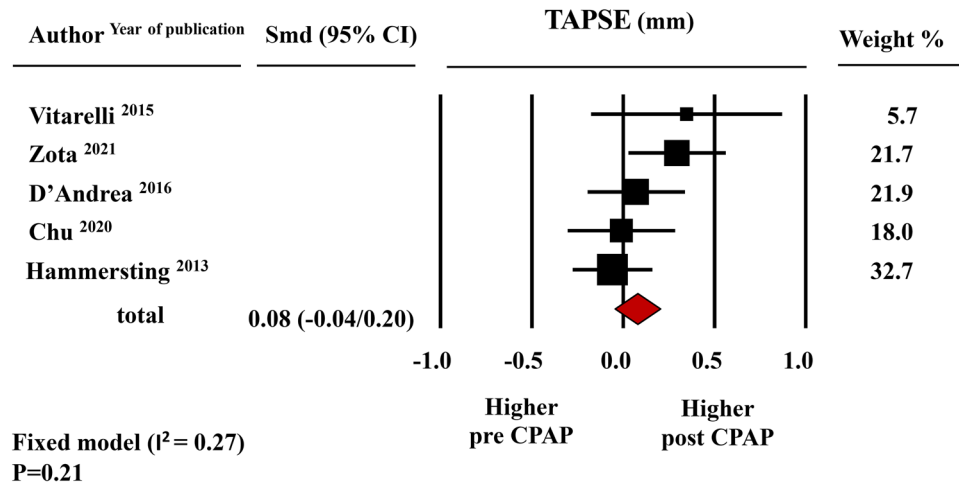


FIGURE 4 Forest plot for standard means difference (SMD) of tricuspid annular plane systolic excursion (TAPSE) in patients with OSA before and after CPAP (fixed model, $I^2 < 0.75$). Relative weight of each study is reported on the right side. CI = confidence intervals

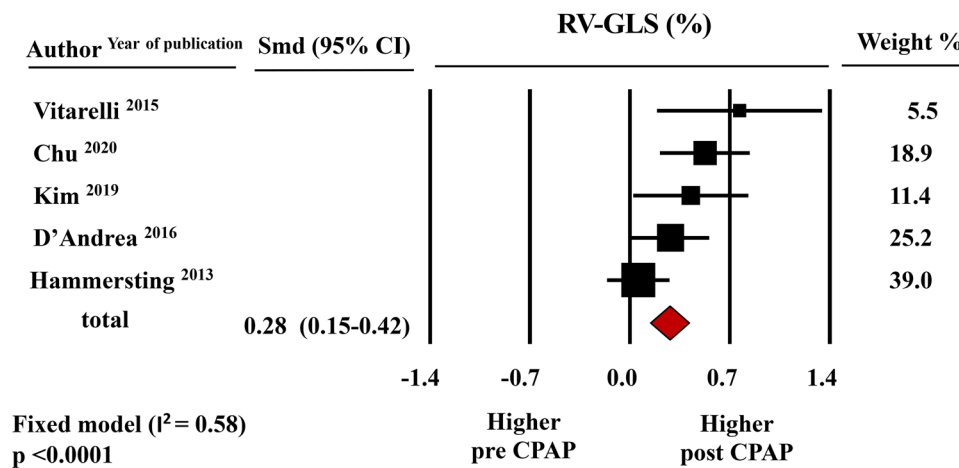


FIGURE 5 Forest plot for standard means difference (SMD) of right ventricular global longitudinal strain (RV GLS) in patients with OSA before and after CPAP (fixed model, $I^2 < 0.75$). Relative weight of each study is reported on the right side. CI = confidence intervals

0.26 ± 0.12 , CI $-0.5/-0.02$, $p = .04$). Right ventricular wall thickness (three studies) varied from 5 ± 0.70 to 4.6 ± 0.4 mm after CPAP (SMD -0.30 ± 0.01 , CI $-0.49/-0.12$, $p < .0001$). The average pooled values of E/e' (four studies) were 9.5 ± 0.7 at baseline and 8.5 ± 1.6 after follow-up (SMD -0.23 ± 0.15 , CI $-0.53/0.07$, $p = .13$). Pulmonary artery systolic pressure (six studies) varied from 28.2 ± 3.9 to 23.7 ± 2.5 mm Hg (SMD -0.21 ± 0.07 , CI $-0.34/-0.09$, $p < .001$).

3.4 | Publication bias

The presence of single study effect was excluded at sensitivity analysis; a relevant publication bias was not present for studies reporting LV and RV GLS before and after CPAP treatment. As for GLS the difference pre- and post- CPAP treatment was still present after correction for publication bias (SMD: -0.47 , CI: $-0.63/-0.33$, $p < .001$) (Figure S1). This was also the case for RV GLS (SMD: -0.19 , CI: $-0.31/-0.07$, $p < .001$).

4 | DISCUSSION

OSA represents an important independent predictor of CV outcomes and mortality.^{27,28} In this clinical setting, CPAP therapy has been reported to be effective in reducing CV and all-cause mortality.^{29,30} The event rate, however, remains high in patients with severe OSA even after CPAP treatment, indicating the need for additional therapy. A recent trial by Labarca and coworkers investigating the effects of CPAP in preventing CV events in OSA patients, failed to show a significant reduction in CV outcomes in patients with moderate-to-severe OSA and concomitant established CV disease (coronary or cerebrovascular disease).¹⁴ Moreover, a large meta-analysis including 5817 OSA patients did not reveal any association between CPAP therapy and CV mortality, myocardial infarction, unstable angina, heart failure, stroke, and atrial fibrillation.³¹ These controversial results may be related to multiple factors, including OSA severity, insufficient compliance to CPAP, comorbidities such as obesity, diabetes and CV dis-

eases, inadequate inhibition of the renin-angiotensin-aldosterone system, sympathetic nervous system, oxidative stress and inflammation. Cardiac remodeling has been suggested to play a determinant role in the therapeutic effect of CPAP in OSA patients.

Our meta-analysis provides several important findings that will be further discussed: (I) a traditional parameter of LV systolic function such as LVEF significantly increased during CPAP therapy; (II) LV mechanics, evaluated by GLS, significantly improved after CPAP treatment; and (III) a conventional parameter of RV systolic function such as TAPSE did not significantly change after CPAP; (IV) GLS showed a better sensitivity than TAPSE in detecting the improvements of RV mechanics after CPAP.

No significant differences in LVEF were reported in patients with different degrees of OSA severity^{18,21,24} and even between controls and OSA patients.^{20,21} These findings may be related to differences in baseline characteristics of the population study, such as obesity, BP and glucose regulation, as well as duration of CPAP therapy (hours per night, total duration of therapy during follow-up) and compliance to therapy. Of note, our meta-analysis shows that LVEF significantly increased after CPAP therapy; this parameter was in the normal range independently of OSA severity in the majority of studies^{18–24} and LVEF deterioration from mild, to moderate, and severe OSA was only reported by Hammerstingl and coworkers¹⁷ These authors reported that LVEF improved in patients with moderate and severe OSA, but not in mild OSA; in other studies, LVEF values before and after CPAP treatment have been reported in the OSA group as a whole.^{19,21}

LVEF represents a traditional measurement of LV systolic function that is faced by several limitations including geometric assumptions, limited reproducibility and relatively low sensitivity in detecting subclinical systolic dysfunction.

GLS is devoid of the majority of these limitations and represents a more robust parameter of systolic function compared to LVEF; GLS may detect more subtle changes in LV systolic function³² and has a better predictive value than LVEF.³³ Consistent data are available about GLS in OSA patients and document the negative influence of OSA on LVGLS in these patients.^{18,20} GLS, as well as circumferential and radial strains, have been reported to progressively worsen in patients with mild to moderate and severe OSA, in front of similar LVEF values.²¹ It should be pointed out, however, that Vitarelli and coworkers found no differences in circumferential and radial strain, but only in GLS, among these subgroups.¹⁸

Our meta-analysis confirmed that LV GLS significantly improved in CPAP-treated OSA patients. It is worth of noting that a couple of studies included in the present meta-analysis showed that GLS was able to detect an improvement in LV systolic function after CPAP therapy in patients with unchanged LVEF.^{21,22} Zota and coworkers revealed the importance of CPAP overnight time (threshold 240 min/night) and showed that shorter periods failed to improve GLS, whereas CPAP night periods > 240 min significantly improved LV GLS; this was not the case for LVEF.²⁴ The authors also demonstrated that a 6-week CPAP therapy tended to increase GLS by three units in OSA patients, even when CPAP night period was < 240 min/night; the increment did not reach the statistical significance probably due to the small sam-

ple size.²⁴ Of note, in this study LVEF did not change more than one unit over a 6 weeks of CPAP therapy with night-time periods longer than 240 min. Kim and coworkers showed that circumferential strain, in addition to GLS, significantly improved after CPAP treatment.²¹

Over the last decades, numerous studies have reported a RV remodeling in OSA patients. The majority of studies were focused on conventional echocardiographic parameters of RV structure and function (RV diameters, TAPSE, FAC and s'). Unfortunately, these parameters are less sensitive than RV GLS in detecting subtle changes in RV systolic function. Our meta-analysis suggested that RV GLS improved after CPAP therapy in OSA patients whereas this was not the case for TAPSE. A significant reduction in free-wall RV longitudinal strain in patients with moderate-severe OSA and concomitant TAPSE, s' and 3D RV volumes enlargement has been documented.¹⁹ This study also reported that RV GLS and 3D RVEF were the major predictors of severe OSA (AHI > 30). In accordance with these findings, Kim and coworkers documented a significant reduction in RV area, improvement of FAC and s' , besides an increase in RV GLS in OSA patients after 3-month CPAP therapy.²² No difference in TAPSE, but still a reduced RV GLS in OSA patients has been reported by other studies.^{17,20} The improvement of RV after CPAP may be explained by the decreased RV volume (structural remodeling) and increased 3D RV ejection fraction (functional remodeling).

The mechanism underlying CPAP-induced improvement of both LV and RV functions, may be related to the reduced negative intrathoracic pressure and decreased hypoxia and hypercapnia periods. The first mechanism results in a decrease in venous return, in LV afterload and RV preload. The second one results in inhibition of sympathetic activity leading to a decrease in peripheral vasoconstriction, arterial stiffness, hypoxic pulmonary artery vasoconstriction and RV afterload.

As for clinical implications, our meta-analysis underlines the need to include LV and RV GLS evaluation in the routine echocardiographic assessment of OSA patients, in order to define the level of LV and RV subclinical damage. LV and RV GLS appear to be more sensitive than conventional echocardiographic parameters (LVEF and TAPSE, respectively) in detecting subtle changes of LV and RV systolic function in OSA patients either at baseline and, more importantly, during CPAP treatment and in providing a reliable evaluation of therapy efficacy and patient's compliance.

5 | LIMITATIONS

Major limitations of this meta-analysis include: (I) predominantly observational studies were included, the majority of them with a limited number of OSA patients; only one randomized, sham-controlled trial was included²²; (II) inconsistency about age, BMI, OSA duration and severity, and comorbidities; (III) duration of CPAP therapy was heterogeneous among studies; and (iv) RV changes were not evaluated independently of OSA-induced LV remodeling.

Furthermore, it was not possible to evaluate the impact of CPAP compliance on the myocardial strain. Finally, no data about the effects

of CPAP therapy on clinical outcomes and cardiovascular events during the follow-up period were provided.

6 | CONCLUSIONS

The assessment of LV and RV mechanics through GLS provides a novel insight into subclinical impairment of LV and RV systolic functions, which are not detectable by conventional echocardiographic parameters in OSA patients. Our results showed that LV and RV GLS may provide a reliable information about CPAP-induced ventricular functional improvement in OSA patients. This might be helpful not only to detect subclinical changes, but also to assess the efficacy and compliance to CPAP therapy. This specific treatment may prevent the progression of LV and RV abnormalities and reverse these changes before severe and irreversible structural and functional alterations develop. Future longitudinal investigations on the relationship between LV and RV mechanical changes and outcomes are essential in order to determine the predictive value of LV and RV GLS in OSA patients as well as the impact of CPAP therapy on the association between cardiac mechanics and outcomes.

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AUTHOR CONTRIBUTIONS

Marijana Tadic – writing the review paper. Elisa Gherbesi – statistical analysis, collection of data, literature review.

Andrea Faggiano - statistical analysis, collection of data, literature review. Carla Sala - statistical analysis, collection of data, literature review. Stefano Carugo - detailed review with constructive remarks that substantially. Cesare Cuspidi – conceptualization, methodology, writing the review paper, supervision.

CONFLICT OF INTEREST

The authors have no competing interests.

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SUPPORTING INFORMATION

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