



## META-ANALYSIS

# Obstructive sleep apnea and right ventricular function: A meta-analysis of speckle tracking echocardiographic studies

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## Abstract

The authors investigated the association between obstructive sleep apnea (OSA) and right ventricular (RV) systolic dysfunction through a meta-analysis of echocardiographic studies providing data on RV mechanics as assessed by longitudinal strain (LS). A systematic search was conducted using PubMed, OVID-MEDLINE, and Cochrane library databases to search English-language review papers published from inception to March 31, 2022. Only studies reporting data on RV free-wall or global LS in patients with OSA of different severity and non-OSA controls were reviewed. Data of interest were pooled to obtain standard means difference (SMD) with 95% confidence interval (CI). The meta-analysis included 628 participants (436 with OSA and 192 controls) from eight studies. Compared to controls, RV free wall LS was significantly reduced in the pooled OSA group (SMD  $1.02 \pm .33$ , CI: .17/1.24,  $P < .002$ ); this was also the case for RV global LS (SMD:  $.72 \pm .11$ , CI: .50/.93,  $P < .0001$ ). Notably, compared to patients with mild-OSA those with moderate and severe OSA exhibited significantly lower RV free-wall LS and global LS values; this was not the case for tricuspid annular plane excursion. In conclusions, both RV free-wall and global LS are impaired in patients with OSA; deterioration of these indices, unlike TAPSE, was already evident in the early stages and was related to the severity of the syndrome. Thus, RV myocardial strain should be considered to be included in echocardiographic evaluation of OSA patients in order to detect subclinical cardiac damage in these patients regardless of its degree of severity.

## KEYWORDS

meta-analysis, obstructive sleep apnea, right ventricular strain, tricuspid annular plane excursion

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## 1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent manifestation of chronic sleep breathing disorders in the general population; age, male sex and obesity are the main risk factors.<sup>1,2</sup>

This condition is caused by a recurrent upper-airway collapse during sleep resulting in blood oxygen desaturation, brain arousal, sympathetic activation, negative intrathoracic pressure, pulmonary, and systemic hypertension.<sup>3,4</sup>

A large amount of evidence supports the view that OSA is associated with an increased risk of non-fatal and fatal cardiovascular (CV) events as well as all-cause mortality.<sup>5,6</sup> One of the mechanisms underlying the poor CV prognosis in patients with OSA is the development of structural and functional cardiac changes triggered by the hemodynamic, hormonal and inflammatory consequences of nocturnal arterial desaturation.<sup>7,8</sup>

Over the past few decades, hundreds of studies and their meta-analyses, have examined the effects of OSA on subclinical cardiac damage targeting left ventricular hypertrophy (LVH) and LV dysfunction.<sup>9,10</sup> A recent meta-analysis of 39 studies including 5550 patients with OSA and 2329 non-OSA controls from 39 studies suggested that the risk of LVH in patients with OSA was 70% higher than in non-OSA counterparts and linked to the OSA severity.<sup>11</sup>

Less evidence exists on the impact of this breathing disorder on right ventricular (RV) structure and function despite that pulmonary hypertension may occur in 20%–40% of OSA patients.<sup>12,13</sup> This relies mainly on the fact that an accurate evaluation of RV morphology and function by conventional echocardiographic techniques remains challenging due to its complex geometric shape and difficulties to reliably assess RV myocardial performance.<sup>14</sup> Studies targeting RV function in the OSA setting based on conventional echocardiographic parameters reported mixed results. Some authors pointed out that patients with OSA frequently present RV structural and functional alterations,<sup>15,16</sup> others, on the contrary, failed to reveal significant morpho-functional alterations of this cardiac chamber.<sup>17,18</sup>

In the last decade, RV strain, a parameter measuring myocardial deformation, has been recognized to provide a better evaluation of RV dysfunction than conventional echocardiographic parameters and, for this reason, it has been incorporated into contemporary echocardiographic guidelines for the assessment of RV performance.<sup>19</sup>

Starting from these premises, we carried out a meta-analysis of speckle tracking echocardiographic (STE) studies assessing RV myocardial deformation in patients with OSA with the aim to ascertain whether RV strain outperforms with respect to conventional parameters in identifying RV dysfunction even in less severe OSA forms.

## 2 | METHODS

### 2.1 | Search and study selection

The present research was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)

guidelines.<sup>20</sup> Pertinent literature was systematically scrutinized to identify all papers addressing RV strain in OSA, as assessed by 2D-3D STE echocardiography.

The PubMed (PubMed, <http://www.bdpubmed.com/>), OVID-MEDLINE (<http://www.embase.com/>), and Cochrane library (<http://www.thecochranelibrary.com/>) databases were analyzed to search English-language review papers published from the inception up to March 31, 2022.

Studies were identified by using Me-SH terms and crossing the following terms: “obstructive sleep apnea”, “sleep quality”, “sleep disordered breathing”, “cardiac damage”, “right ventricle”, “systolic dysfunction”, “global longitudinal strain”, “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 A.F.) assessed retrieved abstracts and full text of these studies to establish eligibility according to the inclusion criteria mentioned below. A third reviewer (C.C.) resolved disagreements on study judgments. Data extraction were performed by one reviewer (E.G.) and independently checked by another reviewer (A.F.).

Main inclusion criteria were: (1) English review papers published in peer-reviewed journals; (2) studies providing data on both RV mechanics and TAPSE by standard and STE echocardiography; (3) minimum set of clinical/demographic data. Specific exclusion criteria were: (1) studies with less than 10 patients with OSA, (2) studies conducted in children and adolescents (age < 18 years); (3) studies in patients with overt cardiac diseases, namely, heart failure with reduced LVEF and acute coronary artery disease.

### 2.2 | Definition of OSA

In the selected studies respiratory events were scored according to the recommendations of major guidelines as follows: apneic events were defined as complete cessation or  $\geq 90\%$  decrease in airflow from baseline value for  $\geq 10$  s. Hypopnea was variously classified as a 30%–50% decrease in airflow lasting at least 10 s. The apnea/hypo-apnea index (AHI) cut-off of  $\geq 5$  events/h was used to select patients with OSA in all studies. OSA severity was defined as follows: mild (AHI 5–15), moderate (AHI 16–30); or severe (AHI > 30).

### 2.3 | Echocardiography

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

## 2.4 | Statistical analysis

The outcome of the meta-analysis was to compare alterations in RV systolic function expressed as continuous variables (ie, RV longitudinal strain and tricuspid annular plane excursion), as assessed by standard and STE echocardiography, in patients with OSA and in their non OSA counterparts, as well as in patients with increasing degrees of OSA severity. To this purpose, a pooled analysis of echocardiographic parameters was performed using fixed or random effects models by Comprehensive Meta-Analysis Version 2, Biostat, Englewood, NJ, USA.

Standard means difference (SMD) with 95% confidence interval (CI) was calculated in order to evaluate the statistical difference of variables in OSA patients and controls. The limit of statistical significance was set at  $P < .05$ . Demographic and clinical data provided by selected studies are expressed as absolute numbers, percentage, mean  $\pm$  standard deviation (SD), mean  $\pm$  standard error (SE) or inter-quartile range.

Heterogeneity was estimated by using I-square, Q and tau-square values; random or fixed effect models were applied when heterogeneity across studies ( $I^2$ ) was higher or lower than 75%, respectively. Meta-regression analysis was used to determine the impact of AHI upon RV mechanics.

Publication bias was assessed by using the funnel plot method 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.

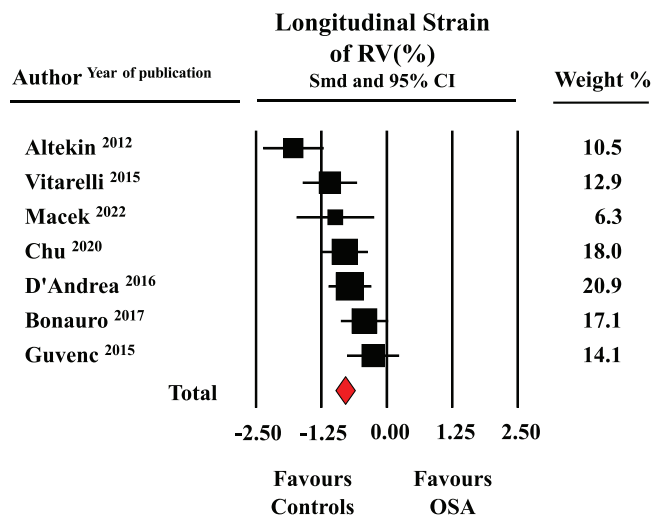
## 3 | RESULTS

The first literature screening identified a total of 711 papers. After the initial search of titles and abstracts, 661 papers were excluded and 50 were reviewed; of these, eight studies<sup>21–28</sup> fulfilled the inclusion criteria and comprised sufficient data to be enclosed in the present meta-analysis (Figure S1).

The Newcastle-Ottawa Score, used for assessing the quality of the studies, ranged from 7 to 9, the mean score being 7.5. Therefore, no study was excluded based on its limited quality ([http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)).

### 3.1 | Characteristics of the studies

Overall, 628 participants (436 with OSA and 192 controls) were included in eight studies performed in two continental areas (Europe = 6, Asia = 2). No difference was noted between groups with regard to age ( $52 \pm 2.9$  vs.  $51 \pm 3.2$  years,  $P = .13$ ), systolic ( $129 \pm 4.9$  vs.  $124 \pm 3.1$  mm Hg,  $P = .07$ ) and diastolic ( $80 \pm 3.1$  vs.



**FIGURE 1** Forest plot for standard means difference (SMD) of free wall or global longitudinal strain of right ventricle (RV) in controls and patients with OSA (fixed model,  $I^2 = 70\%$ ,  $P < .0001$ ). Relative weight of each study is reported on the right side. CI, confidence intervals

$78 \pm 2.1$  mm Hg,  $P = .14$ ) blood pressure (BP). Pooled BMI was higher in OSA patients than in controls ( $30.2 \pm 1.27$  vs.  $29.9 \pm .75$  kg/m<sup>2</sup>,  $P < .01$ ).

Table 1 shows the main demographic, clinical and echocardiographic characteristics of selected studies comprising year of publication, OSA sample size, age, prevalence of men, body mass index (BMI), clinical setting, RV longitudinal strain (LS), RV LS type, TAPSE, AHI, RVEF, time saturation  $< 90\%$  (min), minimal saturation O<sub>2</sub>(%) and STE method.

The vast majority of studies enrolled patients with OSA of different severity referred to out-patient or in-hospital sleep clinics for known or suspected sleep disordered breathing. All but one, studies enrolled individuals without OSA as control group.

Average age range of OSA patients was 47–68 years,<sup>21,25</sup> 69% of participants were men. Mean BMI varied from  $26.0 \pm 2.4$  kg/m<sup>2</sup> to  $34.0 \pm 7.0$  kg/m<sup>2</sup>.<sup>25</sup>

### 3.2 | RV systolic function in the whole OSA patients group versus controls

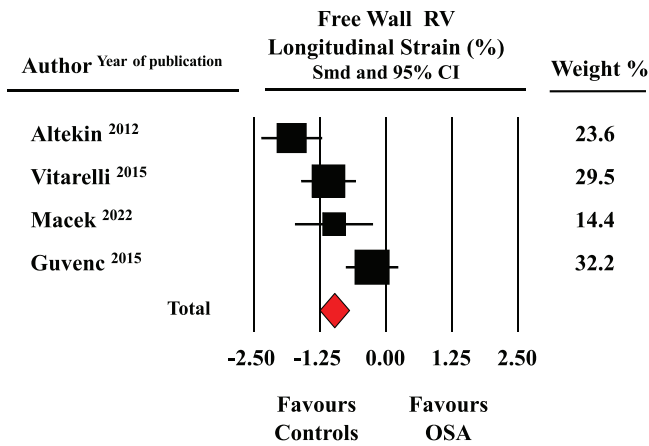
TAPSE was lower in OSA patients than in non-OSA counterparts (SMD:  $-.64 \pm .29$ , CI:  $-1.20/-0.07$ ,  $P = .03$ , data from six studies) (Figure S2). The results of the meta-analysis of seven studies providing overall data on RV free-wall or global LS (Figure 1) and four studies targeting only RV free-wall LS (Figure 2) showed that both these strain indexes were less negative (ie, worse) in the pooled OSA group compared to non-OSA counterparts (SMD:  $.79 \pm .10$ , CI:  $.61/.98$ ,  $P < .0001$ ; and SMD:  $1.02 \pm .33$ , CI:  $.17/1.24$ ,  $P < .002$ ; respectively).

**TABLE 1** Summary of seven studies targeting right ventricular strain in patients with obstructive sleep apnea, as assessed by echocardiography, published from 2012 to 2022

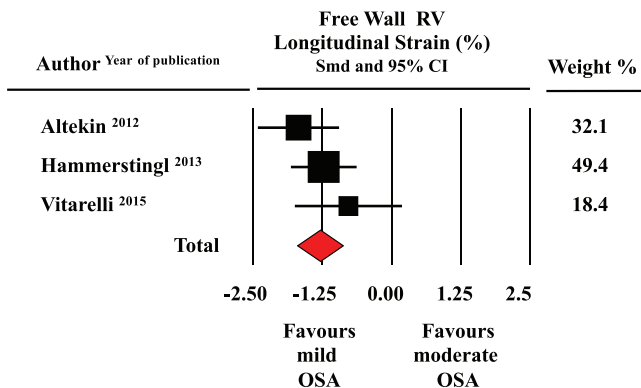
Author (reference)	Year publication	OSA sample size (n)	Age (years)	Sex (% male)	BMI (kg/mq)	RV-LS (%)	RV-LS type	TAPSE (mm)	RVEF (%)	AHI (h)	Time SatO2 < 90% (min)	Minimal SatO2 (%)	Setting	STE method
Altekin <sup>21</sup>	2012	58	47 ± 6	78	29 ± 3	-25.0 ± 5.3	FW	20.9 ± 1.9	na	30.0 ± 7.0	na	na	Mild to severe OSA without CV disease	2D
Hammerstingl <sup>22</sup>	2013	82	63 ± 12	63	31 ± 6	-16.9 ± 7.5	FW	24.8 ± 5.9	na	31.0 ± 2.7	na	na	Mild to severe OSA with prevalent CV disease	2D
Guvenc <sup>23</sup>	2015	41	48 ± 9	66	32 ± 5	-21.9 ± 6.4	FW	22.0 ± 4.0	na	38.0 ± 12.0	na	na	Moderate to severe OSA without CV disease	2D
Vitarelli <sup>24</sup>	2015	37	48 ± 10	38	28 ± 6	-20.2 ± 4.5	FW	17.8 ± 4.0	44.4 ± 8.0	36.0 ± 7.0	18.1 ± 9.0	75.5 ± 12.2	Mild to severe OSA without comorbidities	3D
D'Andrea <sup>25</sup>	2016	55	68 ± 11	70	34 ± 7	-13.8 ± 5.2	Tot	22.6 ± 2.0	na	35.0 ± 15.0	23.5 ± 33.9	82.6 ± 7.8	Mild to severe OSA without CV disease	2D
Bonauro <sup>26</sup>	2017	59	54 ± 11	83	33 ± 7	-20.9 ± 4.9	Tot	23.5 ± 3.3	55.2 ± 8.0	42.0 ± 24.0	na	na	OSA without CV disease	2D
Chu <sup>27</sup>	2020	71	48 ± 8	73	26 ± 2.4	-18.8 ± 5.9	Tot	20.0 ± 2.2	41.5 ± 5.0	44.0 ± 17.0	22.7 ± 12.5	75.3 ± 8.2	Mild to severe OSA without CV disease	2D
Macek <sup>28</sup>	2022	33	na	na	na	-27.8 ± 5.8	FW	na	na	na	na	na	Mild to severe OSA with prevalent HTN	2D

Data are presented as absolute numbers, percentage, mean ± SD.

Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index; RV-LS, right ventricular longitudinal strain; FW, free wall; Tot, total; TAPSE, tricuspid annular plane systolic excursion; RVEF, right ventricular ejection fraction; AHI, apnoea/hypo-apnoea index; CV, cardiovascular; HTN, hypertension; STE, speckle tracking echocardiography.



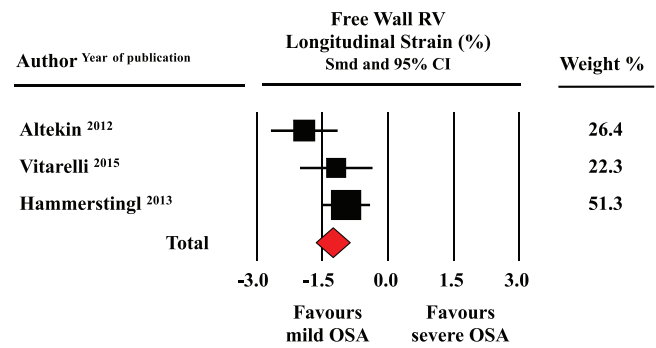
**FIGURE 2** Forest plot for standard means difference (SMD) of free-wall longitudinal strain of right ventricle (RV) in controls and patients with obstructive sleep apnea (OSA) (random model,  $I^2 = 81\%$ ,  $P = .002$ ). Relative weight of each study is reported on the right side. CI, confidence intervals



**FIGURE 3** Forest plot for SMD of free-wall longitudinal strain of right ventricle (RV) in patients with mild and moderate OSA (fixed model,  $I^2 = 10\%$ ,  $P < .0001$ ). Relative weight of each study is reported on the right side. CI, confidence intervals

### 3.3 | RV systolic function according to OSA severity

TAPSE did not differ between patients with mild and those with moderate OSA (SMD:  $.28 \pm .19$ , CI:  $-.10/.66$ ,  $P = .14$ , data from three studies) as well as between patients with mild versus their counterparts with severe OSA (SMD:  $.85 \pm .57$ , CI:  $-.27/1.96$ ,  $P = .14$ , data from three studies). On the contrary, RV free-wall LS was found to be less negative (ie, worse) in patients with moderate OSA than in mild OSA (SMD:  $1.29 \pm .21$ , CI:  $.87/1.70$ ,  $P < .0001$ , data from three studies) (Figure 3) as well as in patients with severe OSA than in those with mild OSA (SMD:  $1.26 \pm .20$ , CI:  $.87/1.65$ ,  $P < .0001$ , data from three studies) (Figure 4). Similar findings were observed for RV global LS (data not shown). Finally, both TAPSE and RV free-wall LS did not differ statistically when patients with moderate OSA were compared with those with severe OSA.



**FIGURE 4** Forest plot for SMD of free-wall longitudinal strain of right ventricle (RV) in patients with mild and severe OSA (fixed model,  $I^2 = 51\%$ ,  $P < .0001$ ). Relative weight of each study is reported on the right side. CI, confidence intervals

### 3.4 | Additional echocardiographic parameters

RV diastolic diameter ( $36.7 \pm 1.2$  vs.  $33.5 \pm 1.5$  mm,  $P < .001$ ), RV wall thickness ( $4.7 \pm .20$  vs.  $4.0 \pm .06$  mm,  $P = .03$ ) and systolic pulmonary arterial pressure (PAPs) ( $35.3 \pm 2.7$  vs.  $25.9 \pm 1.5$  mm Hg,  $P < .001$ ) were higher in patients with OSA than in controls.

### 3.5 | Correlation analyses

Meta-regression analysis between AHI and SMD in free or global RV LS was performed to assess the impact of such variable on RV mechanics. As shown in Figure S3, we found a significant relationship between AHI ( $P = .0003$ ) with SMD in RV strain (ie, high SMD values in RV strain between patients with OSA and non-OSA controls were associated with OSA severity).

### 3.6 | Publication bias

The presence of a single study effect was excluded at sensitivity analysis; a relevant publication bias was not present for studies reporting TAPSE, RV LS in controls and OSA patients. As for RV free-wall or global LS the difference between the whole OSA group and controls was still present after correction for publication bias (SMD:  $.65$ , CI:  $.46/.84$ ,  $P < .01$ ) (Figure S4).

## 4 | DISCUSSION

Data about the impact of OSA on right ventricular remodeling and mechanical changes are scarce, as the majority of studies have been focused on left ventricular structural and functional changes induced by this syndrome. The present meta-analysis provides insightful information about this topic in a large number of OSA patients. The following aspects should be addressed, in particular: (i) global RVLS and free-wall RVLS were significantly impaired in OSA patients compared

to controls; (ii) a trend to a gradual deterioration in global RVLS and free-wall RVLS from patients with mild, to moderate and severe OSA was present; a statistically significant difference was found between mild versus moderate and mild versus severe OSA, but not between moderate versus severe OSA; and (iii) the traditional parameter of RV systolic function, TAPSE, was different between OSA patients and controls, but not between the various degrees of OSA severity.

Thus, RVLS may recognize subtle changes in RV function and mechanics that are undetectable by traditional echocardiographic parameters such as TAPSE,  $s'$  and FAC.<sup>29</sup> In the clinical setting, detection of subclinical RV dysfunction may be useful for preventing and monitoring frequent complications of OSA, such as RV failure and pulmonary hypertension.<sup>30,31</sup> RVLS represents an excellent predictive parameter in various CV conditions related not only to RV (pulmonary hypertension, congenital heart diseases), but also to primary diseases of LV (heart failure, valvular heart disease, coronary artery disease, arterial hypertension).<sup>32,33</sup> Thus, RVLS may represent an important clinical and prognostic parameter in OSA patients and a reliable parameter for monitoring the therapeutic effect of continuous positive airway pressure (CPAP), in patients with moderate and severe stages of disease. The current study showed that RVLS is a reliable index for detection of subclinical RV damage and its progression in the different OSA stages.

Our meta-analysis showed that TAPSE was reduced in OSA patients compared with controls, but this parameter was not able to differentiate the progressive stages of OSA syndrome. It should be pointed out, however, that the majority of studies included in this meta-analysis failed to find any difference in TAPSE,  $s'$  or fractional area change (FAC) between OSA patients and controls<sup>22–28</sup> and only Altekin and coworkers found that TAPSE was significantly worsened in patients with moderate and severe OSA compared to controls.

As for RVLS and free-wall RVLS, the majority of studies reported that these parameters were reduced in OSA patients compared to controls; only Güvenç and coworkers did not find significant differences in these two parameters between groups, in front of higher 3D RV volumes in OSA patients.<sup>23</sup> It should be pointed out that Güvenç and coworkers investigated RV mechanics in OSA patients living at high altitudes, and possibly subjected to adaptive changes to altitude-related chronic hypoxemia, as suggested by the same authors.<sup>23</sup> Not all studies, unfortunately, provided separated results for free-wall RVLS and global RVLS: this point is of importance if we consider that global RVLS includes interventricular septum, that is mostly part of the LV, although it contributes to approximately 30% of RVEF.<sup>34</sup> It should be pointed out, however, most of the studies providing free-wall RVLS values showed a significant reduction of this parameter in OSA patients compared to controls,<sup>21,24,28</sup> as well as its deterioration from mild to severe OSA type, although the difference between moderate and severe OSA patients did not reach the statistical significance.<sup>21,22</sup> Some authors reported a positive correlation between AHI and RVLS, thus supporting a relationship between OSA severity and RV mechanical impairment.<sup>21,22,24</sup> This point is of clinical significance, as it allows to define OSA stages, in alternative to complex polysomnographic tests during follow-up of these patients.

Determination of RVLS may have potential impacts on OSA treatment. Some studies, indeed, showed that CPAP significantly improved RVLS.<sup>24,25,27</sup> Interestingly, D'Andrea and coworkers reported that non-invasive ventilation (NIV) induced a significant deterioration of RV mechanics – global and free-wall RVLS, whereas CPAP improved RVLS.<sup>25</sup> The authors explained the reduction of RVLS as the result of an abnormal RV diastolic filling, due to increased RV afterload and reduced venous return during NIV.<sup>25</sup> TAPSE and  $s'$ , conventional parameters of RV systolic function, were unchanged during NIV or CPAP therapy; this finding further underlines the importance of a sensitive parameter such as RVLS in monitoring RV function in treated OSA patients and rapidly assessing the therapeutic effect of NIV or CPAP. The RVLS changes, indeed, were detected after a relatively short period of CPAP therapy (4–6 months).<sup>24,25</sup>

In some studies 3D echocardiography was used to evaluate RV volumes and RVEF, but this technique yielded controversial results. Some authors, indeed, found significantly higher RV volumes and normal RVEF in OSA patients<sup>23</sup> whereas others reported a gradual increment in RV volumes and a reduction in RVEF from mild to severe OSA patients<sup>24</sup>; finally, some investigators failed to find any difference in RV volumes and RVEF between controls and OSA.<sup>26</sup> Vitarelli and coworkers showed that 3D RVEF and RVLS were better predictors of severe OSA (AHI > 30) than TAPSE and FAC.<sup>24</sup> This underlines the importance of RVLS in prediction of severe OSA, as 2D RV strain analysis appears more available in clinical practice than 3D echocardiography.

This study potentially has large clinical importance, as the large number of studies reported an important prognostic impact in large number of different cardiovascular conditions (heart failure, valvular heart disease, coronary artery disease, pulmonary hypertension, COVID-19, congenital cardiac diseases, different cardiomyopathies, etc.).<sup>32,33</sup> These data are still not available for OSA patients. However, it is reasonable to hypothesize that RV GLS should have a significant prognostic importance in OSA patients before or during any type of treatment.

## 5 | LIMITATIONS

The present meta-analysis has several limitations that need to be addressed. The majority of included studies had a limited number of OSA patients with heterogeneous average age, BMI, OSA severity, and comorbidities. Sex differences in RVLS values were not taken into account in any of included studies, even though large studies indicate significantly higher values in women compared to men.<sup>35</sup> Clinical outcomes and CV events during follow-up were not provided, in particular no study reported a relevant clinical aspect, such as the effects of CPAP therapy in OSA patients. A certain heterogeneity between the various studies included in the meta-analysis in terms of age and clinical characteristics should be also mentioned as a potential limitation. However, the number of studies on this topic is very limited and more homogeneous population regarding demographic and clinical characteristics is currently not feasible.



## 6 | CONCLUSIONS

In summary, our meta-analysis demonstrated that global and free-wall RVLS were significantly lower in OSA patients than in controls. RVLS was related with severity of OSA despite lack of statistical significance between moderate and severe OSA. Conventional parameters of RV systolic function, TAPSE, s' and FAC, were generally not able to diagnose subclinical changes in RV function between OSA patients and controls, as well as between OSA stages, or to detect subtle improvement during CPAP therapy. Overall, the performance of RVLS may have important clinical impacts in diagnosing and monitoring OSA patients. Larger longitudinal studies with longer follow-up are highly needed in order to prove these hypotheses.

### ACKNOWLEDGMENT

No funding for this study.

### CONFLICT OF INTEREST

There is no conflict of interest related to this study.

### AUTHOR CONTRIBUTIONS

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

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Tadic M, Gherbesi E, Faggiano A, Sala C, Carugo S, Cuspidi C. Obstructive sleep apnea and right ventricular function: A meta-analysis of speckle tracking echocardiographic studies. *J Clin Hypertens.* 2022;24:1247-1254. <https://doi.org/10.1111/jch.14550>