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Clinical Research

Assessment of Right Ventricular Function in Obstructive Sleep Apnea Syndrome and Effects of Continuous Positive Airway Pressure Therapy: A Pilot Study

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See editorial by Raisinghani, et al., pages 821-822 of this issue.

ABSTRACT

Background: It is known that obstructive sleep apnea syndrome (OSAS) can affect right ventricular (RV) performance even in the absence of systemic hypertension and other known cardiac or obstructive pulmonary disease. The purpose of the present study was to assess RV function in OSAS using 3-D echocardiography and speckle tracking echocardiography (STE) and evaluate changes after continuous positive airway pressure (CPAP) treatment.

Methods: Thirty-seven patients with OSAS without comorbidities and thirty control subjects were studied using 3-D echocardiography and STE. Fifteen patients underwent CPAP therapy and were studied before and after treatment. RV 3-D ejection fraction was calculated. Peak systolic strain was determined. RV dyssynchrony was defined as SD of the 6 time to peak systolic strain values.

Results: 3-D RV ejection fraction was lower and RV dyssynchrony was greater in patients with moderate-severe OSAS compared with control

RÉSUMÉ

Introduction : On sait que le syndrome de l'apnée obstructive du sommeil (SAOS) peut affecter la performance du ventricule droit (VD) même en l'absence d'hypertension systémique et d'autres maladies cardiaques ou pulmonaires obstructives. Le but de la présente étude était d'évaluer la fonction du VD lors du SAOS à l'aide de l'échocardiographie 3D et de l'échocardiographie *Speckle Tracking* (suivi de pixel; EST) et les changements après le traitement par pression positive expiratoire continue (CPAP).

Méthodes : Trente-sept patients souffrant du SAOS sans comorbidités et 30 sujets témoins ont été étudiés à l'aide de l'échocardiographie 3D et de l'EST. Quinze patients ont subi la thérapie CPAP et ont été étudiés avant et après le traitement. La fraction d'éjection du VD en 3D a été calculée. La déformation systolique maximale a été déterminée. La dyssynchronie du VD a été définie comme étant suérieure de 6 fois l'ET des valeurs maximales de déformation systolique.

Obstructive sleep apnea syndrome (OSAS) is the most common form of sleep-disordered breathing characterized by excessive daytime sleepiness, choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, and sleep monitoring demonstrating 5 or more obstructive apneas/hypopneas per hour during sleep.[1,2] Definitions of OSAS are based on respiratory and neurophysiologic indices but recent reports showed that cardiovascular sequelae could be more important because complications such as coronary artery disease, heart failure, systemic and pulmonary hypertension (PH), and arrhythmias increase morbidity and mortality. Studies on this subject have assessed the effects of OSAS on the left ventricle (LV) and tested the effect of OSAS treatment with continuous positive airway pressure (CPAP) on LV changes.[3-7] Early determination of right ventricular (RV) dysfunction in patients with OSAS and PH is also important in preventing progression to heart failure even in the absence of overlapping chronic lung disease, morbid obesity, or left-sided heart disease.[8-10] However, data on RV dysfunction and structural changes in patients with OSAS are not always clear as the effects of CPAP therapy on this chamber.[9-11]

Moreover, because the right ventricle has a complex crescent shape and is wrapped around the LV, it is difficult to assess RV functions with conventional 2-dimensional (2D) echocardiography. The 2D speckle tracking echocardiography (STE) is a new 2D technique that assesses myocardial deformation and deformation rate by tracking speckles in the

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subjects in the presence and absence of pulmonary hypertension. 3-D RV ejection fraction and RV dyssynchrony were independently associated with apnea-hypopnea index. Patients treated with CPAP had significant changes in RV parameters.

Conclusions: 3-D RV ejection fraction and RV dyssynchrony were abnormal in OSAS patients compared with control subjects and associated with OSAS severity. RV 3-D STE abnormalities improved after chronic application of CPAP.

Résultats : La fraction d'éjection du VD en 3D était plus faible et la dyssynchronie du VD était plus grande chez les patients souffrant du SAOS modéré à grave que chez les sujets témoins en présence ou en l'absence d'hypertension pulmonaire. La fraction d'éjection du VD en 3D et la dyssynchronie du VD étaient indépendamment associées à l'index d'apnées-hypopnées. Les patients traités par CPAP montraient des changements significatifs dans les paramètres du VD.

Conclusions : La fraction d'éjection du VD en 3D et la dyssynchronie du VD étaient anormales chez les patients souffrant du SAOS comparativement aux sujets témoins et associées à la gravité du SAOS. Les anomalies du VD en 3D à l'EST s'amélioraient après l'application à long terme du CPAP.

myocardium on greyscale (B-mode) images and can be used to evaluate global and regional myocardial wall strain.[12,13] Three-dimensional echocardiography (3DE) is also regarded as a promising tool for quantifying RV volumes and function with good correlation to magnetic resonance imaging (MRI), and is a robust, accurate, and reproducible modality for RV volume and function measurements.[14]

In the literature, although there are several studies in which the effects of CPAP therapy on RV myocardial performance in patients with OSAS were determined with conventional echocardiography,[11] there are only few reports that assessed them with STE[12,13] and 3DE[14] and a comparative analysis has not been performed. We hypothesized that in patients with OSAS the use of new echocardiographic techniques improves the assessment of RV dysfunction. The purpose of the present study was twofold: first, we aimed to evaluate the association between OSAS severity and these new RV function parameters, and second to establish whether RV function abnormalities are reversible with CPAP therapy.

Methods

For detailed methodological information and statistical analysis, see the *Methods* section of the Supplementary Material.

A cohort of 37 sleep apnea patients without comorbidities and 30 control subjects were examined with polysomnography[15] and echocardiography. Established echocardiographic criteria were used for assessment of right chambers.[16-23] Three-dimensional echocardiographic images (Fig. 1) were stored digitally for off-line analysis using dedicated software. STE acquisitions were also obtained, with analyses being performed retrospectively and off-line. The general principles that underlie STE modalities have been previously described.[24-29]

All patients underwent overnight polysomnography using a standard technique. Apnea-hypopnea index (AHI) was defined as the number of apneas and/or hypopneas per hour. OSAS was defined as $\geq$ 5 AHI events per hour in the presence of clinical symptoms suggesting OSAS.[15,30,31] On the basis of AHI, patients were classified[1,2] into mild (> 5 to < 15), moderate (> 15 to < 30), and severe OSAS ($\geq$ 30). Fifteen compliant patients with OSAS who had CPAP and complete 3-D and strain analyses were studied before and after treatment. After baseline echocardiography, patients were instructed to use the CPAP device every night for at least 6 hours. Patients received nightly CPAP therapy for at least 4 months and echocardiography was repeated the day after the last nocturnal CPAP treatment while patients were awake.

Results

Thirty-seven of 44 initially evaluated OSAS patients were included in the study. 3DE images of the right ventricle were successfully analyzed in 41 of 44 patients. Longitudinal 2D RV strain measurement from all segments because of adequate tracking quality was possible in 42 of 44 patients. 3-D feasibility was 93%, and 2D strain feasibility was 95%. Tricuspid regurgitation to estimate right-sided pressure was found in 37 of 44 patients (84%). The intraobserver and interobserver reproducibility of 3-D and strain parameters was shown to be acceptable. Intraobserver variability (mean absolute difference between measurements) was 4.4 $\pm$ 2.1% for 3-D RV end-diastolic volume, 5.2 $\pm$ 2.5% for 3-D RV end-systolic volume, 6.8 $\pm$ 3.7% for 3-D RV ejection fraction (RVEF), 8.2 $\pm$ 3.8% for global RV longitudinal strain (RVLS), 4.7 $\pm$ 3.1% for global free-wall RVLS, and 7.1 $\pm$ 3.2% for RV dyssynchrony (SD of the 6 time to peak systolic strain values; SD6). Interobserver variability was 4.8 $\pm$ 3.8% for 3-D RV end-diastolic volume, 7.7 $\pm$ 3.6% for 3-D RV end-systolic volume, 7.1 $\pm$ 4.1% for 3-D RVEF, 8.8 $\pm$ 4.2% for global RVLS, 5.3 $\pm$ 3.9% for global free-wall RVLS, and 7.9 $\pm$ 3.1% for RV SD6.

The baseline characteristics of OSAS patients and control subjects are given in Table 1. No patient had systemic hypertension. There was a statistical trend for significance for body mass index (BMI; $P = 0.06$) to be greater in the severe OSAS group compared with the control group. Daytime hypercapnia (partial pressure of arterial carbon dioxide $\geq$ 45 mm Hg) was present in 7 of 37 (18.9%) patients with OSAS. Three of them had BMI $\geq$ 30.

Echocardiographic parameters

LV ejection fraction was not significantly different in OSAS patients and control subjects, and was in normal limits (Table 2). RV systolic pressure (RVSP), pulmonary vascular resistance, and RV wall thickness were greater in severe OSAS than in control subjects. 3-D RVEF and strain values in patients with moderate-severe OSAS showed a highly significant difference from normal. There was no significant difference in 3-D and RV strains between patients with mild OSAS and control subjects.

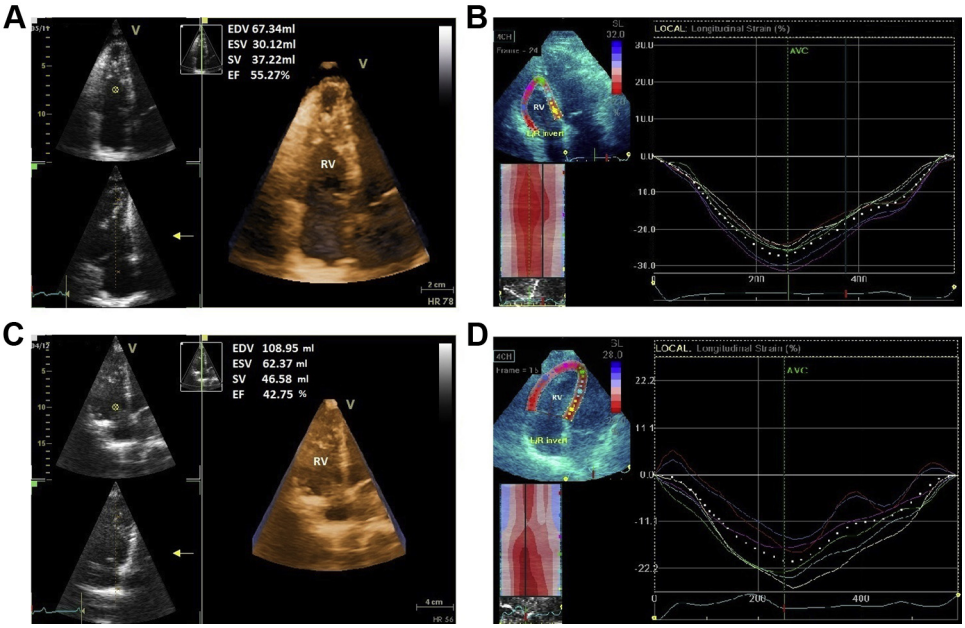

Figure 1. Three-dimensional echocardiography and speckle tracking imaging in (**A, B**) a normal subject and (**C, D**) a patient with obstructive sleep apnea syndrome and lower 3-D right ventricular ejection fraction (RVEF) and right ventricular longitudinal strain (RVLS). (**A**) 3-D RVEF = 55%; (**B**) RVLS = −26%; (**C**) 3-D RVEF = 42%; (**D**) RVLS = −18%.

PH (RVSP > 40 mm Hg) was found in 20 patients and normal RV pressure values in 17 patients. Increased RV wall thickness in patients compared with control subjects was found in 18 of 20 patients with PH and 2 of 17 patients with normal pulmonary pressures. 3-D RVEF and RV SD6 were lower (Fig. 2) in patients with OSAS and PH compared with the control group ($P < 0.0001$), in patients with OSAS and PH compared with patients with OSAS and normal pulmonary artery pressure ($P < 0.005$), and in patients with OSAS and normal pulmonary pressure compared with normal control subjects ($P < 0.005$).

A significant correlation (Fig. 3) was obtained between RV SD6 and RVSP ($r = 0.71$; $P < 0.005$) and between RV SD6 and AHI ($r = 0.77$; $P < 0.001$). AHI and RVSP were correlated with RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), RVLS, RV SD6, and 3-D RVEF. After adjusting for RVSP, correlations between AHI and strain 3-D RV indices remained significant.

Receiver operating characteristic curves showed the potential of various echocardiographic parameters (Table 3) to be associated with OSAS severity (AHI > 30). 3-D RVEF had the greatest area under the curve (0.89) followed by RV SD6 (0.86), RVLS (0.82), RVSP (0.76), ratio of RV to LV end-diastolic diameters (4-chamber view; 0.73), RVFAC (0.70), TAPSE (0.69), and pulmonary acceleration time (0.68). By combining RV SD6 + 3-D RVEF, the area under the curve was significantly improved to 0.91 ($P < 0.005$ compared with RV SD6, $P < 0.001$ compared with RVLS).

Multiple linear regression analysis using a forward stepwise regression model was performed using AHI as a dependent variable and age, BMI, RVFAC, TAPSE, RVSP, RVLS, RV SD6, and 3-D RVEF as independent variables. Results demonstrated (Supplemental Table S1) that OSAS severity (AHI) was associated with age ($P = 0.017$), BMI ($P = 0.037$), RVSP ($P = 0.041$), TAPSE ($P = 0.026$), RV SD6 ($P = 0.005$), and 3-D RVEF ($P = 0.001$). In multivariate analysis, after adjusting for significant predictors in univariate analysis, RV SD6 ($\beta = 0.43$; $P = 0.006$) and 3-D RVEF ($\beta = -0.57$; $P = 0.003$) were independently related to AHI.

RV 3-D STE and polysomnographic data before and after CPAP

The effects of chronic 4-month CPAP therapy on the polysomnographic data and echocardiographic indexes of RV function are depicted in Table 4. The CPAP was used for 6 ± 0.3 hours per night (range, 5-6.1 hours). The BMI, blood pressure, and heart rate of the patients remained unchanged. The group treated with CPAP had a significant decrease in pulmonary artery systolic pressure, total pulmonary vascular resistance, RV SD6, and RV volumes and significant increase in 3-D RVEF. The AHI decreased significantly (4.2 ± 1.6 events per hour). An increase in mean and lowest arterial oxygen saturations, and a decrease in the duration of oxygen saturation < 90% were also seen.

Discussion

The results of the present study are as follows: (1) overall in patients with OSAS, RV longitudinal strain and 3-D RVEF decreased and volumes increased in parallel with changes in segmental dyssynchrony in the presence and absence of PH; (2) RV dyssynchrony and 3-D RVEF had a greater association with OSAS severity compared with other echocardiographic indices of RV dysfunction; and (3) CPAP therapy tended to restore the uniformity of RV wall contraction with reduction of RV volumes.

Table 1. Patient demographic characteristics

	Control subjects (n = 30)	Mild OSAS (n = 10)	P*	Moderate OSAS (n = 8)	P†	Severe OSAS (n = 19)	P‡
Age, years	46.2 ± 13.4	47.9 ± 10.3	ns	47.6 ± 9.1	ns	48.1 ± 10.2	ns
Sex: male/female	11/19	4/6	ns	3/5	ns	7/12	ns
Smoker, n (%)	9 (30)	3 (30)	ns	2 (25)	ns	6 (31.6)	ns
Body surface area, cm^2	1.82 ± 0.15	1.89 ± 0.26	ns	1.90 ± 0.23	ns	1.92 ± 0.27	ns
Body mass index, kg/m^2	26.4 ± 4.3	26.9 ± 5.8	ns	27.4 ± 5.5	ns	28.2 ± 6.3	ns
Heart rate, beats per minute	69.3 ± 9.2	70.6 ± 7.5	ns	71.9 ± 6.8	ns	70.4 ± 6.1	ns
Systolic blood pressure, mm Hg	120.1 ± 7.9	123.1 ± 8.1	ns	121.5 ± 7.8	ns	122.4 ± 8.1	ns
Diastolic blood pressure, mm Hg	74.4 ± 5.7	77.1 ± 6.1	ns	76.6 ± 6.5	ns	78.5 ± 6.3	ns
NYHA FC I, n (%)	-	9 (90)	-	7 (88)	ns§	13 (68)	ns¶
NYHA FC ≥ II, n (%)	-	1 (10)	-	1 (13)	ns§	6 (32)	< 0.05¶
Fasting blood glucose, mg/dL	96.2 ± 9.5	100.7 ± 9.4	ns	99.8 ± 9.6	ns	101.8 ± 10.8	ns
Cholesterol, mg/dL	168.1 ± 10.8	171.2 ± 8.7	ns	169.5 ± 9.8	ns	171.8 ± 9.9	ns
LDL cholesterol, mg/dL	87.2 ± 11.3	89.2 ± 14.1	ns	88.3 ± 12.8	ns	89.5 ± 15.4	ns
HDL cholesterol, mg/dL	39.4 ± 2.4	37.6 ± 3.4	ns	38.2 ± 3.1	ns	35.3 ± 3.9	ns
Triglyceride, mg/dL	124.6 ± 15.1	124.9 ± 17.2	ns	126.8 ± 16.4	ns	122.9 ± 18.2	ns
PaO_2, mm Hg	93.4 ± 2.1	90.2 ± 2.6	ns	81.9 ± 2.2	< 0.05	68.4 ± 1.4	< 0.01
$PaCO_2$, mm Hg	34.3 ± 1.8	35.3 ± 0.9	ns	40.9 ± 0.7	< 0.05	49.1 ± 1.6	< 0.01
HCO_3, mm Hg	24.3 ± 2.4	24.9 ± 2.6	ns	26.8 ± 3.0	< 0.05	28.2 ± 2.7	< 0.01
Awake SaO_2, %	94.5 ± 2.2	93.1 ± 2.6	ns	94.2 ± 2.3	ns	93.1 ± 2.2	ns
AHI, events per hour	3.8 ± 1.4	7.1 ± 1.9	< 0.05	19.8 ± 2.7	< 0.01	58.9 ± 9.1	< 0.001
Mean nocturnal SaO_2, %	93 ± 4.8	91.9 ± 12.2	ns	90.4 ± 11.3	ns	83.1 ± 12.1	0.04
Minimal SaO_2, %	91 ± 3.9	81.5 ± 12.1	0.03	79.2 ± 11.8	0.02	70.8 ± 12.4	< 0.005
Time SaO_2 < 90%, minutes‖	0.6 ± 0.2	2.6 ± 0.9	0.04	4.9 ± 1.4	0.03	31.9 ± 16.4	< 0.005

AHI, apnea-hypopnea index; HCO_3, serum bicarbonate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant; NYHA FC, New York Heart Association functional class; OSAS, obstructive sleep apnea syndrome; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SaO_2, saturation of arterial oxygen.

* Mild vs control subjects.

† Moderate vs control subjects.

‡ Severe vs controls.

§ Moderate vs mild.

¶ Severe vs mild.

‖ Duration that oxygen saturation was < 90%.

Table 2. RV echocardiographic parameters in OSAS patients and controls

	Control subjects (n = 30)	Mild OSAS (n = 10)	P*	Moderate OSAS (n = 8)	P†	Severe OSAS (n = 19)	P‡
RV/LV	0.66 ± 0.17	0.68 ± 0.19	ns	0.71 ± 0.28	ns	1.21 ± 0.25	< 0.01
LVEF, %	61.1 ± 6.4	60.9 ± 7.8	ns	62.4 ± 6.8	ns	59.4 ± 7.3	ns
RVFAC, %	49 ± 12	47 ± 13	ns	45 ± 12	ns	35 ± 10	< 0.05
TAPSE, mm	23 ± 6	21 ± 3	ns	18 ± 4	< 0.05	16 ± 4	< 0.05
RVMPI	0.25 ± 0.06	0.27 ± 0.09	ns	0.33 ± 0.10	ns	0.49 ± 0.12	< 0.05
RVWT, mm	3.97 ± 0.42	4.03 ± 0.58	ns	4.34 ± 0.53	ns	5.62 ± 0.69	< 0.05
TV S_a, cm/s	12.6 ± 2.5	11.9 ± 2.9	ns	9.2 ± 3.3	< 0.05	7.8 ± 3.3	< 0.05
TV E_a, cm/s	15.3 ± 3.4	14.7 ± 3.3	ns	10.8 ± 3.1	< 0.05	8.2 ± 3.1	< 0.05
TV E/E_a	8.4 ± 0.8	8.7 ± 1.1	ns	9.1 ± 1.2	ns	14.2 ± 1.7	< 0.05
RVSP, mm Hg	22 ± 3	25 ± 6	ns	35 ± 11	< 0.05	46 ± 11	< 0.01
PVR, Wood units	1.3 ± 0.5	1.5 ± 0.7	ns	1.9 ± 0.8	< 0.05	2.8 ± 1.1	< 0.01
TR grade > 1, n (%)	4 (13.3)	5 (50)	< 0.05	6 (60)	< 0.01	7 (36.8)	< 0.05
TR grade > 2, n (%)	0	1 (1)	ns	3 (37.5)	0.006	12 (63.2)	0.002
PAT, ms	126.4 ± 21.1	112.1 ± 16.1	ns	95.6 ± 10.2	< 0.05	85.8 ± 11.2	< 0.05
Global RVLS, %	−24.2 ± 3.4	−23.6 ± 3.7	ns	−22.9 ± 3.8	ns	−19.1 ± 3.7	< 0.005
Global FW RVLS, %	−25.6 ± 5.5	−23.7 ± 4.1	ns	−20.5 ± 4.1	< 0.01	−18.2 ± 4.9	< 0.001
RV SD6, ms	28 ± 15	36 ± 20	ns	55 ± 22	< 0.001	112 ± 33	< 0.0005
3-D RVEDV, mL	76 ± 14	82 ± 18	ns	92 ± 20	< 0.005	108 ± 36	< 0.001
3-D RVESV, mL	35 ± 8	44 ± 9	ns	51 ± 12	< 0.005	65 ± 21	< 0.001
3-D RVEF, %	53.2 ± 7.1	50.6 ± 8.1	ns	45.9 ± 8.4	< 0.005	40.4 ± 8.5	< 0.0001

E, inflow early diastolic velocity; E_a, annular early diastolic velocity; FW, free wall; LV, left ventricle; LVEF, left ventricular ejection fraction; OSAS, obstructive sleep apnea syndrome; PAT, pulmonary acceleration time; PVR, pulmonary vascular resistance; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVFAC, right ventricular fractional area change; RVLS, right ventricular longitudinal strain; RV/LV, ratio of RV to LV end-diastolic diameters (4-chamber view); RVMPI, right ventricular myocardial performance index; RVSP, right ventricular systolic pressure; RVWT, right ventricular wall thickness; S_a, annular systolic velocity; SD6, dyssynchrony (SD of the 6 time to peak systolic strain values); TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV, tricuspid valve.

* Mild OSAS vs control subjects.

† Moderate OSAS vs control subjects.

‡ Severe OSAS vs control subjects.

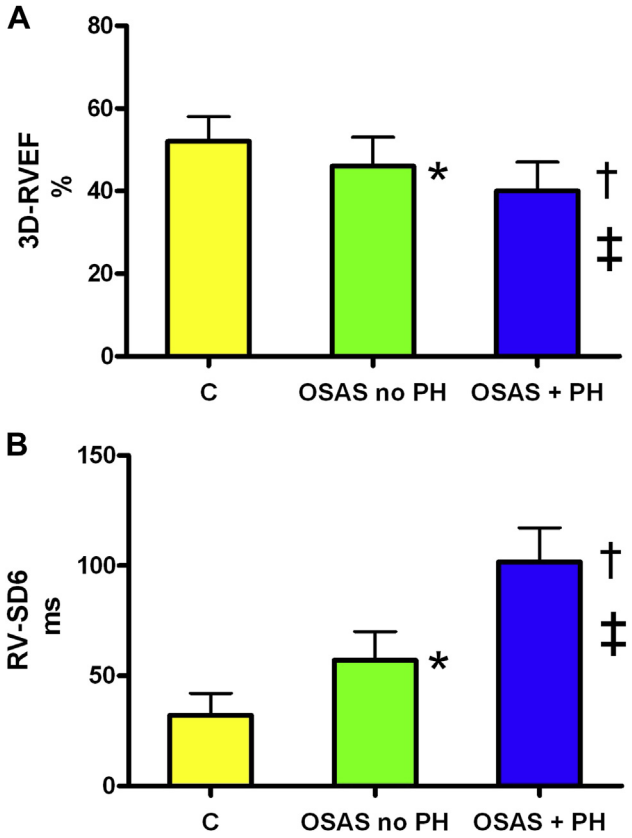

Figure 2. Bar graph depicting (**A**) 3-D right ventricular ejection fraction (3-D RVEF), and (**B**) and right ventricular dyssynchrony (RV SD6) in normal control subjects (C), patients with obstructive sleep apnea syndrome (OSAS) and normal pulmonary artery pressure (OSAS no pulmonary hypertension [PH]), and patients with OSAS and PH (OSAS + PH). * $P < 0.005$, OSAS no PH vs control subjects; † $P < 0.005$, OSAS + PH vs OSAS no PH; ‡ $P < 0.0001$, OSAS + PH vs controls.

Previous studies

The association between RV impairment and OSAS severity has been previously reported using various echocardiographic techniques and indices.[8-14,32-36] In a sample of patients without cardiovascular and pulmonary diseases, a significant negative correlation between AHI and RV fractional area change has been reported.[32] It was also shown that RV wall thickness was significantly greater in patients with sleep-disordered breathing than in control subjects after multivariable adjustment[10,35] albeit transthoracic echocardiography had limitations that preclude making measurements in some subjects in whom the structure being studied cannot be well visualized. In normotensive patients it was found that severe OSAS frequently caused daytime PH in the absence of either significant heart or lung disease and it was speculated that daytime PH could have a precapillary component related to repetitive hypoxia-reoxygenation leading to pulmonary vasoconstriction and vascular remodelling.[36] Other authors,[13] using strain echocardiography, found a subclinical RV dysfunction in OSAS patients even in the absence of PH and pathologies that could have adverse effects on RV functions. Recently it has also been reported[14] that OSAS was an independent predictor of lower 3-D-determined RVEF.

Present study

To our knowledge, this is the first study to show that OSAS severity is associated with impaired RV function determined at the same time using 3-D volumes and deformation parameters. The stress imposed by OSAS on the RV is a combination of increased afterload (increase in pulmonary vascular resistance) and increased preload (increase in RV end-diastolic 3-D volume), and these findings explain the decrease in 3-D RVEF. RV dilatation and dysfunction was significantly correlated with AHI and the severity and number of apneas. The pulmonary pressures were borderline normal in 45% of our patients, and this is in accordance with literature data that showed that in selected patients with "pure" OSAS (ie, without clinically identifiable cardiopulmonary disease) the prevalence of PH was 25%-50% and that OSAS patients with PH appear to have higher pulmonary vascular reactivity to intermittent hypoxia than OSAS patients without PH.[36-38]

RV dysfunction was present in normotensive patients but was more marked in those with PH. RV dyssynchrony leads to a worsening of RV function, and this effect is independent from QRS duration.[29] It represents presumably an exacerbation of the natural chamber dyssynchrony that we would expect as the ventricle contracts against increased pulmonary vascular resistance, and the fact that it decreases with therapy

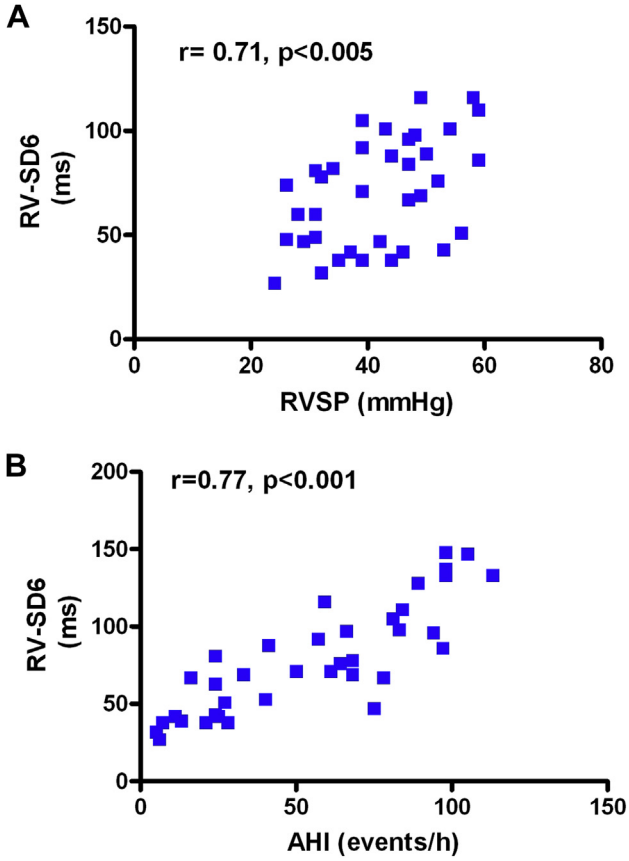

Figure 3. Significant relationship (**A**) between right ventricular dyssynchrony (RV SD6) and right ventricular systolic pressure (RVSP), and (**B**) between RV SD6 and apnea-hypopnea index (AHI).

Table 3. Results of receiver-operating characteristic curves comparing different RV echocardiographic parameters for their accuracy of association with OSAS severity (AHI > 30)

Parameter	AUC	95% CI	*P*	Cutoff	Sensitivity	Specificity
PAT	0.68	0.54-0.92	0.09	86 ms	68	61
TAPSE	0.69	0.52-0.98	0.07	14 mm	71	66
RVFAC	0.70	0.53-0.95	0.08	38%	70	63
RV/LV	0.73	0.49-0.91	0.07	1.07	72	67
RVSP	0.76	0.61-0.93	0.05	43 mm Hg	78	69
RVLS	0.82	0.66-0.88	0.03	−17%	85	75
RV SD6	0.86	0.71-0.93	0.03	73 ms	87	75
3-D RVEF	0.89*	0.74-0.99	0.02	44%	89	77

AHI = apnea-hypopnea index; AUC, area under the curve; CI, confidence interval; LV, left ventricle; OSAS, obstructive sleep apnea syndrome; PAT, pulmonary acceleration time; RV, right ventricle; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; RVLS, right ventricular longitudinal strain; RV/LV, ratio of RV to LV diameters (apical four-chamber view); RVSP, right ventricular systolic pressure; SD6, dyssynchrony (standard deviation of the 6 time to peak systolic strain values); TAPSE, tricuspid annular plane systolic excursion.

* $P < 0.05$ compared with RV SD6; $P < 0.005$ compared with RVLS.

might be explained by the concomitant decrease in pulmonary vascular resistance. However, after adjusting for RVSP, correlations between AHI and strain 3-D RV indices remained significant, therefore these results suggest that RV impairment is in part independent of PH.

Table 4. Change in RV indices and polysomnographic data in a subset of 15 patients who had chronic CPAP therapy for 4 months

	Before CPAP therapy	After CPAP therapy	*P*
RVFAC, %	36 ± 11	38 ± 12	ns
TAPSE, mm	15 ± 4	17 ± 4	ns
RVMPI	0.52 ± 0.11	0.49 ± 0.13	ns
RVWT, mm	5.69 ± 0.63	4.98 ± 0.87	ns
TV S_a (cm/s)	7.2 ± 3.1	7.5 ± 3.2	ns
TV E_a (cm/s)	8.3 ± 3.4	9.1 ± 3.5	< 0.05
TV E/E_a	13.8 ± 1.7	12.6 ± 1.4	ns
RVSP, mm Hg	37 ± 11	25 ± 11	< 0.05
PVR, Wood units	2.7 ± 1.2	1.8 ± 0.7	< 0.05
Global RVLS, %	−19.3 ± 4.6	−20.7 ± 4.8	< 0.01
Global FW RVLS, %	−18.1 ± 4.8	−19.6 ± 5.3	< 0.01
RV SD6, ms	107 ± 33	74 ± 19	< 0.005
3-D RVEF, %	40.2 ± 8.3	46.3 ± 8.6	< 0.001
3-D RVEDV (mL)	105 ± 38	86 ± 23	0.006
3-D RVESV (mL)	62 ± 19	45 ± 12	< 0.001
AHI, events per hour	57.9 ± 9.1	4.2 ± 1.6	< 0.001
Mean nocturnal SaO_2, %	88.7 ± 12.1	92.7 ± 12.9	0.002
Minimal SaO_2, %	70.9 ± 11.7	88.2 ± 13.3	< 0.001
Time SaO_2 < 90%, minutes*	31.6 ± 17.1	2.6 ± 2.7	< 0.001
Awake SaO_2, %	92.9 ± 2.2	94.7 ± 1.6	ns

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; E, inflow early diastolic velocity; E_a, annular early diastolic velocity; FW, free wall; ns, not significant; PVR, pulmonary vascular resistance; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVFAC, right ventricular fractional area change; RVLS, right ventricular longitudinal strain; RVMPI, right ventricular myocardial performance index; RVSP, right ventricular systolic pressure; RVWT, right ventricular wall thickness; S_a, annular systolic velocity; SaO_2, saturation of arterial oxygen; SD6, dyssynchrony (SD of the 6 time to peak systolic strain values); TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.

* Duration that oxygen saturation was < 90%.

The possible pathophysiological explanation of increased preload in OSAS could be[32,33,38] the significant gradient of negative intrathoracic pressure that is required to open the upper airway during the obstructive episodes and causes a high venous return. A second possible mechanism might be the fluid retention (as suggested in our patients by the increase in partial pressure of arterial carbon dioxide and HCO_3) that increases preload and RV end-diastolic volume and thus contributes to RV dyssynchrony. Carbon dioxide either directly, or via a humoural pathway, might activate a sodium-retaining mechanism within the kidney, and in this regard the most likely candidate is the sodium-hydrogen exchanger involved in the buffering of respiratory acidosis in the luminal membrane of proximal tubules.[39] After treatment, RV volumes decreased, ejection fraction increased, RV strain improved, and these findings indicate RV structural changes as a consequence of functional remodelling. The BMI, blood pressure, and heart rate of the patients remained unchanged. Accordingly, the observed improvements seem to be associated with CPAP, which reduces the apneic episodes and the sympathetic activity. It has been reported[32] that therapy with CPAP is analogous to the effects of chronic β-blockade in heart failure but is achieved nonpharmacologically by reducing the oxygen demand and increasing the oxygen supply. After 4 months of treatment, changes in the RV diastolic wall velocities and wall thickness were also observed in our patients but results were variable and with less significance compared with systolic volumetric and deformation parameters and it is possible that improvement in diastolic function requires more time than 4 months.

In the published reports the prevalence of hypercapnia associated with OSAS ranges from 11% to 43%[40] and is greater in patients with morbid obesity and severe sleep apnea and patients with chronic obstructive pulmonary disease together with OSAS ("overlap syndrome"). Because both patients with chronic obstructive pulmonary disease and patients with morbid obesity (BMI ≥ 40) were excluded from this study, we had few hypercapnic patients with OSAS who satisfied the criteria of Obesity Hypoventilation Syndrome (OHS), when obesity was defined as BMI ≥ 30. The causal relationship between OSAS and OHS is beyond the aim of our study. However, it has been reported[40] that OHS can also occur without significant OSAS and the pathogenesis of daytime hypercapnia might be directly linked to OSAS per se in a subset of patients with OSAS. Furthermore, in the present study multiple linear regression analysis showed that RV SD6 and 3-D RVEF were independently associated with AHI.

We have already shown in previous reports[26,28] that the newer technologies appear to be superior to the older technologies, including RVFAC, TAPSE, and the Myocardial Performance Index (MPI). Compared with RVFAC, the MPI and TAPSE, 3-D RVEF had a stronger correlation with MRI, and the assessment of 3-D RVEF and RV strain allowed a better prediction of unfavourable outcome after atrial septal defect closure.[26] Moreover, assessment of global and regional RV function using 3-D and strain technologies allowed a better prediction of mortality in patients with pulmonary embolism compared with conventional methods.[28] In our cohort of OSAS patients the combined assessment of 3-D RVEF and strain gave us valuable information on RV function and dyssynchrony, allowing a better association with OSAS severity shown in multivariate analysis.

Clinical implications

The present study shows that RV dyssynchrony and 3-D volumetric parameters are more closely associated with the severity of obstructive sleep apnea compared with standard RV function parameters, and improve at 4 months after CPAP therapy. Cardiovascular physicians can use such methodology in patients with OSAS to assess RV structural and functional changes even in the absence of clinically recognizable lung disease or left ventricular disease. Because CPAP was recommended to all patients with severe OSAS or patients with moderate OSAS who complained of severe daytime sleepiness that interfered with daily activities, identification of subclinical RV dysfunction in conditions of intermediate severity could lead to initiation of a therapy that otherwise would not be indicated. Future clinical trials would be helpful to establish the prognostic effect of RV dysfunction in OSAS.

Limitations

Some limitations should be discussed. First, the strain analysis software was applied to the RV assuming that the LV algorithm could be transferred to this chamber. However, even if the reproducibility of this method should be submitted to further validation, 2D strain analysis software was applied to the RV in several clinical studies and reliable results were obtained.[24-26] Second, speckle tracking echocardiography is dependent on frame rate and image resolution. We found frame rates in the range of 60-100 Hz suitable for speckle tracking analysis, that is a lower value than frame rate available with Doppler strain. However, STE might overcome some tissue Doppler limitations with assessment of myocardial thickening in a manner less affected by passive translational motion or tethering. Third, although the problem of variations between the different systems and vendors was recently stressed in terms of speckle tracking analysis,[41] a comparison of data obtained using the various systems would be appropriate and this problem will require collaboration between manufacturers.

Additionally, the 3-D RV endocardial border identification might be challenging especially in obese patients because echo dropouts frequently occur, especially of the anterior wall and outflow tract, and is even more challenging in patients with dilated right ventricles, because the endocardial border might be blurred because of the increased distance from the transducer to the RV wall. However, RV volumes on 3-D echocardiography have been shown to correlate well with MRI-derived RV volumes.[17]

We excluded patients with atrial fibrillation. However, it was shown[42] that peak strain correlates positively with the ratio of the preceding to the prepreceding R-R interval (RR1/RR2) and regional wall motion can be estimated from a single beat based on RR1/RR2 in patients with atrial fibrillation and depressed and preserved ejection fraction.

Moreover, we assessed RV involvement in patients with isolated OSAS without concomitant diseases. The results of this study might not be extrapolated to patients with overt comorbidities or patients with LV dysfunction. The accompanying LV dysfunction might also have additional effects on RV dysfunction via interventricular interactions. However, we already described the effect of OSAS on left ventricular and aortic indices,[7] and a direct independent effect of OSAS on PH[36] and RV myocardial function[10] was previously reported.

Another limitation was the lack of randomization and bias related to patients who received and used CPAP. However, ethical considerations in withholding CPAP for prolonged periods from control groups makes it difficult to schedule randomized trials.

As a further limitation, PH was defined using echocardiographically determined RVSP. However, previous reports showed that pressure estimates using echocardiography correlated well with values derived from cardiac catheterization.[20,21,26] Conflicting reports of the accuracy of echocardiographic measurement of pulmonary artery pressure in recent years could reflect the relative strengths of the reporting laboratories. Actually an accurate assessment of right-sided hemodynamics is possible[43] with integration of several measurements in a complete echocardiographic analysis, just as a right heart catheterization study would be incomplete if only the pulmonary artery systolic pressure were reported.

Last, the relatively small sample size limited our ability to analyze potential clinical benefits in selected subgroups and a larger longitudinal study would be necessary to confirm those data.

Conclusions

Early impairment of RV mechanics in patients with isolated OSAS suggests that it is a response to overload caused by this disease independently of confounders. STE-determined RV dyssynchrony and 3-D volumes were the parameters most closely related with OSAS severity and ventricular subclinical dysfunction. CPAP therapy might prevent the progression of RV abnormalities and reverse these changes before severe structural alterations occur.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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