

# Ventricular Dysfunction in Obstructive Sleep Apnea-Hypopnea Syndrome: In Search of Clinical Significance

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Obstructive sleep apnea-hypopnea syndrome (OSAHS), characterized by repetitive episodes of complete or partial interruption of the airflow during sleep, constitutes a growing healthcare problem. Prevalence in the general population is high and resulting morbidity and mortality, principally attributed to traffic accidents and the development of cardiovascular complications, quite considerable.<sup>1</sup> Although most epidemiologic evidence corresponds to the association of OSAHS with high blood pressure, cerebrovascular disease, and heart failure,<sup>2,3</sup> it has also been associated with cardiovascular disturbances like ischemic heart disease, cardiac arrhythmias, or pulmonary hypertension.<sup>3-6</sup> Moreover, the identification and definition of possible pathogens, and the positive effects of treatment on the cardiovascular system have strengthened the causal relationship.

The relationship between OSAHS and heart failure is especially important due to the high prevalence of both entities and the clinical repercussions. However, we should remember that patients with OSAHS usually present other cardiovascular risk factors such as age, obesity, high blood pressure, diabetes mellitus, or ischemic heart disease, which may constitute confounding factors. Nonetheless, different ways in which OSAHS can cause systolic and diastolic left ventricular dysfunction have been recognized.<sup>2</sup> Intermittent hypoxemia, sympathetic activation and increased ventricular preload and afterload

stand out among these and are all secondary to the repeated obstructive respiratory events. In turn, they activate a series of inflammatory, oxidative, and neurohumoral mechanisms that may contribute to impaired ventricular function.<sup>2,3,7</sup>

In recent years, research studies coincide in reporting that patients with OSAHS frequently present structural and functional alterations of both left and right ventricles. Adequate treatment of the respiratory disturbance through continuous positive air pressure (CPAP) treatment is found to improve or even reverse these, thus reinforcing the hypothetical causal relationship between OSAHS and heart failure.<sup>8-12</sup> Moreover, in patients presenting OSAHS with heart failure and systolic ventricular dysfunction, treatment of the respiratory disturbance has been shown to improve left ventricular systolic dysfunction.<sup>2</sup> Recently, Wang et al<sup>13</sup> reported a prospective study of patients with heart failure and left ventricular systolic dysfunction in which presence of untreated OSAHS was associated independently with an increased risk of death during long-term follow-up. However, despite the wealth of data supporting the relationship between OSAHS and ventricular dysfunction, this has still not attained a degree of relevance necessary to modify clinical procedures.

In the present issue of *Revista Española de Cardiología*, Moro et al<sup>14</sup> present an interesting study in which they determine various echocardiographic parameters that reflect biventricular structure and function in a non-selected group of 103 consecutive patients recently diagnosed with OSAHS. They compare values of echocardiographic and clinical parameters and demographic variables in 2 groups: patients with severe OSAHS and patients with mild or moderate OSAHS. Together with standard echocardiographic measurements (cardiac chamber diameter, wall thickness, left ventricular ejection fraction, and Doppler analysis of transvalvular flow), they calculate the Tei index for both ventricles in each patient. The Tei index constitutes a simple, reproducible, non-invasive method

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of evaluating cardiac function that integrates systolic and diastolic ventricular function and proves relatively independent of heart rate and preload. The index maintains an acceptable relationship with invasive parameters of ventricular function and, specifically, correlates significantly with left ventricular end-diastolic pressure in control groups and in patients with mild-moderate heart failure.<sup>15</sup> In the present study, the authors prove that patients with severe OSAHS have high Tei index scores in both left and right ventricles (indicating worse overall ventricular function) and lower rates of aortic and pulmonary ejection than patients with mild or moderate OSAHS. They find no differences between the 2 groups for echocardiographic variables related with cardiac chamber size or isolated systolic, or diastolic ventricular function. However, they do identify a significant relationship between the apnea-hypopnea index (which quantifies OSAHS severity) and left and right ventricular Tei index values.

If we bear in mind how it is calculated, an increase in the Tei index may be due to alterations in diastolic function parameters or a reduction in ventricular ejection time, reflecting the initial degree of myocardial systolic dysfunction. As Moro et al do not identify any degree of isolated diastolic ventricular dysfunction in the patients studied, they consider that reduced aortic and pulmonary ejection are the principal determinants of their Tei indices. Therefore, Tei index elevation could indicate incipient myocardial systolic dysfunction. Undoubtedly, this is a highly positive aspect of their research, in as much as it verifies the use of a non-invasive alternative for the integrated evaluation of ventricular function in patients with OSAHS, capable of detecting possible subclinical states of impaired ventricular function, present in greater measure in patients with severe OSAHS. In this context, tissue Doppler techniques have improved our capacity to identify early anomalies in both systolic and diastolic function in both ventricles. Shivalkar et al<sup>12</sup> used tissue Doppler to compare echocardiographic findings before and after initiating 6 months CPAP treatment in a group of 43 patients with no known cardiomyopathy and severe OSAHS and 40 similar control patients without OSAHS. By comparison with the control group, patients with OSAHS showed structural and functional changes of right and left ventricles that improved significantly after CPAP.

Although the results reported by Moro et al are not unexpected in the light of studies reported elsewhere, their study has certain limitations and we recommend a cautious interpretation of its findings. The 2 groups of patients with OSAHS (mild or moderate, and severe) are not absolutely homogeneous. They present differences in tobacco and alcohol consumption and neck diameter, and statistically non-significant body mass index. Furthermore, they did not have a control group against which to evaluate echocardiographic

findings obtained in all patients with OSAHS, nor do they state that the echocardiographers were blinded to the results of patients' sleep studies. Finally, we should not forget that the independence of the Tei index with respect to ventricular preload and afterload is relative. In fact, presence of high blood pressure might condition results. For example, for similar degrees of OSAHS severity, a left ventricular Tei index of 0.60 has been reported in a group including 80% of patients with high blood pressure<sup>11</sup> whereas, when all patients had normal blood pressure, the left ventricular Tei index was 0.37.<sup>10</sup> The Tei index is also dependent on preload. However, the index obtained via tissue Doppler has been shown to be less dependent and more precise than that determined by pulsed Doppler, meaning it could constitute an alternative. When the Tei index is used to evaluate ventricular function, we also need to remember that its value depends on the age of the subjects studied. Consequently, normalizing the age of subjects analyzed improves the interpretation of values obtained. This is also important in OSAHS which, although more prevalent in middle-aged men, is also frequent in children and older people.

Finally, the use of Tei indices as indicators of OSAHS severity, as indicated by the authors, is questionable, above all if we consider that it is derived from the apnea-hypopnea index. However, it would be interesting to have access to information about the relationship of the index for both ventricles to the degree of daytime somnolence, sleep disruption, or degree of nocturnal hypoxemia. The frequently-associated morbidity in patients with OSAHS (obesity, high blood pressure, ischemic heart disease, etc) and the fact it can independently cause structural and functional cardiac alterations, amounts to a substantial confounding factor when interpreting index values. Moro et al's study is the first to evaluate the Tei index in a relatively large number of patients with OSAHS. Their results coincide with data obtained by Dursunoglu et al,<sup>11</sup> who evaluated 25 patients with severe OSAHS, almost all with high blood pressure. However, Moro et al's results differ from those obtained in two earlier studies.<sup>10,12</sup> The discrepancies in the values obtained in these studies (Table) are probably largely justified by: *a*) differences in the clinical and demographic characteristics, and associated comorbidity of the patients studied, and *b*) differences in the severity of the syndrome, especially during evolution. Excessive daytime somnolence, a prime symptom of OSAHS, could serve as a marker of the onset of obstructive respiratory events. Moreover, the time lapse from presence of somnolence to effective diagnosis of the illness, a parameter considered in the present study, is included in studies of OSAHS and probably explains much of the differences found in rates of cardiovascular events in populations of patients with OSAHS with similar severity (similar apnea-hypopnea index).

**Left and Right Ventricular Tei Index Values in Patients With Sleep Apnea-Hypopnea Syndrome\***

Author and Bibliographic Reference	N	AHI	LVEF	LV Tei Index	RV Tei Index
Moro et al <sup>14</sup>	103	40 (17)	79 (1)	0.55 (0.17)	0.45 (0.02)
Dursunoglu et al <sup>11</sup>	25	52 (11)	64 (4)	0.60 (0.13)	—
Dursunoglu et al <sup>10</sup>	18	50 (11)	64 (5)	0.37 (0.06)	0.62 (0.09)
Shivalkar et al <sup>12</sup>	43	42 (24)	62 (9)	0.31 (0.06)	0.29 (0.05)

\*LVEF indicates left ventricular ejection fraction; AHI, apnea-hypopnea index; N, number of patients; RV, right ventricle; LV, left ventricle.

On the other hand, as indicated by Moro et al, the Tei index can also be used to evaluate subclinical alterations of the right ventricle. Although pulmonary hypertension has been reported as frequent in patients with OSAHS,<sup>4</sup> possible repercussions on the right ventricle are less well known, so results should be interpreted with caution. In fact, increased Tei index in the right ventricle of patients with observed OSAHS could be due to increased pulmonary artery pressure or incipient left ventricular dysfunction. In 18 patients with moderate-severe OSAHS, Dursunoglu et al<sup>10</sup> reported a right ventricular Tei index of 0.62 (0.09), much greater than the 0.39 (0.05) that was considered the reference. Moreover, they also reported a fall after 6 months CPAP,<sup>10</sup> although this was not statistically significant, when they evaluated the parameter before and after 6 months of treatment.<sup>12</sup>

Currently, indication for CPAP to prevent or treat cardiovascular risk associated with OSAHS is controversial. Indication for treatment continues to be established fundamentally on severity of the syndrome, estimated by the apnea-hypopnea index, and of daytime somnolence. Whether patients without somnolence with mild-moderate OSAHS should be treated for presence of associated cardiovascular morbidity is under debate. The present study confirms findings described elsewhere of preclinical cardiac alterations in subjects without clinical evidence of cardiomyopathy which are more noticeable in subjects with more severe OSAHS. The total or partial reversal of these alterations with adequate treatment of the respiratory disturbance of sleep has also been described. Together with the lack of daytime somnolence frequently experienced by patients with clinical heart failure who present OSAHS,<sup>16</sup> these facts suggest treatment of the syndrome leads to benefits such as reduced cardiovascular morbidity, even with mild degrees of the illness, before preclinical disturbances to the cardiovascular system (like those described in the present article) become evident, or in patients without primary symptoms of OSAHS. However, the benefits of treatment will have to be resolved in future, prospective studies, designed in minute detail, controlled, with large sample sizes and extensive follow-up.

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