Central Sleep Apnea in Left Ventricular Dysfunction
Prevalence and Implications for Arrhythmic Risk

Paola A. Lanfranchi, MD; Virend K. Somers, MD, PhD; Alberto Braghiroli, MD; Ugo Corra, MD; Ermanno Eleuteri, MD; Pantaleo Giannuzzi, MD

Background—The prevalence and characteristics of sleep-disordered breathing in patients with asymptomatic left ventricular (LV) dysfunction are unknown. Therefore, we evaluated the prevalence of sleep-disordered breathing in patients with LV dysfunction without overt heart failure and tested the hypothesis that sleep-disordered breathing is linked to greater hemodynamic and autonomic impairment.

Methods and Results—We studied 47 patients with LV ejection fractions ≤40% without any history of heart failure. Central sleep apnea (CSA), as defined by an apnea-hypopnea index ≥15/h, was present in 26 patients (55%), 17 (36%) of whom had severe CSA (apnea-hypopnea index ≥30/h). Obstructive sleep apnea was evident in 5 patients (11%). The prevalence and severity of CSA were higher in patients with ischemic cardiomyopathy than in patients with nonischemic cardiomyopathy ($P<0.05$). Exercise tolerance and echocardiographic indices of systolic and diastolic function were similar in patients without CSA, with mild CSA, and with severe CSA. Heart rate variability was markedly depressed in patients with CSA ($P<0.05$). Patients with severe CSA also had a higher incidence of nonsustained ventricular tachycardia ($P=0.05$).

Conclusions—CSA is highly prevalent in patients with asymptomatic LV dysfunction. The severity of CSA may not be related to the severity of hemodynamic impairment. Severe CSA is associated with impaired cardiac autonomic control and with increased cardiac arrhythmias. **(*Circulation*. 2003;107:727-732.)**

Key Words: sleep ■ nervous system, autonomic ■ tachyarrhythmias ■ heart failure

In patients with overt heart failure, there is a high prevalence of nocturnal periodic breathing with central apneas (central sleep apnea: CSA).[1–4] CSA is associated with increased arrhythmic risk[3] and may indicate increased mortality in heart failure.[4] Autonomic responses to CSA may contribute to the adverse prognosis in these patients.[2,5] Patients with left ventricular (LV) dysfunction without heart failure also have neurohumoral activation and are at risk for progression to overt heart failure.[6] Sleep-disordered breathing has been invoked as a possible mechanism mediating the progression of cardiac disease in these patients.[7] However, there are no data examining the prevalence and characteristics of sleep-disordered breathing in patients with asymptomatic LV dysfunction.

The goals of the present study were as follows: (1) to evaluate prospectively the prevalence and the nature of sleep-disordered breathing, particularly CSA, in patients with asymptomatic LV dysfunction; and (2) to test the hypothesis that increasing severity of CSA in these patients is associated with greater hemodynamic compromise, impaired cardiac autonomic regulation, and cardiac arrhythmias.

Methods

We prospectively studied consecutive patients referred to the Cardiology Department of the Medical Center of Rehabilitation, Veruno, Italy, between January 1999 and December 2000 who were found to have LV systolic dysfunction due to either ischemic or nonischemic cardiomyopathy. Patients were referred for one of the following: (1) functional evaluation of asymptomatic LV dysfunction, (2) evaluation of chest pain, or (3) rehabilitation after myocardial infarction or cardiac surgery. They were eligible if the echocardiographic left ventricular ejection fraction was ≤40% in the absence of any history or clinical diagnosis of overt heart failure.[8–10] Patients were excluded if they had any of the following: primary valvular heart disease, obstructive lung disease (as demonstrated by a forced expiratory volume per second/forced vital capacity [FEV_1/FVC] <70%), clinical signs of central or peripheral nervous system impairment, a history of stroke, or a history of cocaine or alcohol abuse.

Forty-seven patients (5 women; mean age, 59±12 years; LV ejection fraction, 27±6%) met the entry criteria. Thirty-eight patients (81%) had coronary artery disease (CAD) with a previous myocardial infarction as the presumptive cause of the LV dysfunction. Nine patients (19%) were thought to have idiopathic dilated cardiomyopathy (no CAD). Among patients with CAD, 19 (50%) had a history of a previous coronary revascularization by coronary artery bypass grafting (CABG).

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From the Divisions of Cardiology (P.A.L., U.C., E.E., P.G.) and Pulmonary Disease (A.B.), Fondazione Salvatore Maugeri IRCCS, Veruno, Italy, and the Divisions of Cardiovascular Diseases and Hypertension, Mayo Clinic, Rochester, Minn (P.A.L., V.K.S.).

Correspondence to Paola A. Lanfranchi, Research Center Hôpital Sacré-Coeur, 5400 Boulevard Gouin West, Montréal QC H4J-1C5, Canada. E-mail paola-lanfranchi@CRHSC.umontreal.ca

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All patients gave written, informed consent agreeing to participate in this prospective study, which had been approved by the Science and Ethics Committee of the Institution.

Study Protocol

Patient evaluation included historic data collection, functional classification, Doppler echocardiography, spiroergometric test, thallium-201 myocardial scintigraphy, 24-hour Holter recording, and a sleep study. Functional status was determined according to the New York Heart Association classification.

Echocardiography

A complete 2D echocardiography and Doppler ultrasound examinations were performed using a Hewlett-Packard ultrasound system (model 77729-A or 77622-A).

Spiroergometry Test

Multistage symptom-limited bicycle exercise testing with spirometry was used to evaluate exercise tolerance and peak oxygen consumption (Ergometrics 800S, Sensormedics).

Myocardial Scintigraphy

Nuclear imaging by thallium-201 at rest and after stress was performed to evaluate myocardial perfusion.

24-Hour Ambulatory Electrocardiographic Recording

24-hour ECG recordings were performed (Marquette 8500) to evaluate arrhythmias and to assess heart rate variability. The 24-hour heart rate variability was quantified in the time domain: the mean normal-to-normal R-R interval (NN), the standard deviation of mean NN (sdNN), the standard deviation of all 5-minute mean RR intervals (SDANN), the mean of all 5-minute standard deviations of RR intervals (SD), and the percentage of >50 ms differences between adjacent NN (pNN50) were measured.[11]

Sleep Study

All patients underwent an overnight sleep study by means of an unattended system (Merlin, Healthdyne Inc) that recorded body position, cardiotachography, nasal-oral air flow, chest and abdominal effort, and pulse oximetry. Apnea was defined as cessation of airflow lasting at least 10 s. A central apnea was defined as the absence of flow and thoracoabdominal movements, and an obstructive apnea was defined as the absence of airflow in the presence of thoracoabdominal movements. Hypopnea was defined as ≥50% decrease in the sum of thoracoabdominal movements lasting ≥10 s, followed by a reduction in SaO_2 of at least 4%.[12]

We accepted a threshold of apnea-hypopnea index (AHI) ≥15/h as diagnostic for sleep-disordered breathing[3] and an AHI ≥30/h as severe sleep-disordered breathing.[4] Therefore, we evaluated patients in 3 groups: (1) those without sleep apnea (AHI<15/h), (2) those with mild sleep apnea (AHI=15 to 29/h), and (3) those with severe sleep apnea (AHI≥30/h).

The total duration of ventilation-apnea cycle (cycle-length)[13] was also measured from the first breath following an apnea to the first breath after the following apnea.

Statistical Analysis

All descriptive data are presented as mean±SEM. Differences between groups of patients were compared by one-way ANOVA and, for variables with a non-normal distribution, by Kruskall-Wallis analysis. Frequency of variables was assessed by χ^2 test with a Yates correction. $P<0.05$ was considered significant.

Results

Periodic breathing with CSA occurred in 26 patients (55%). In 17 patients (36%), severe sleep apnea, as defined by an AHI ≥30/h, was noted. Significant obstructive sleep apnea, as expressed by an AHI ≥10, was found in 5 patients (11%; range of AHI, 18 to 49/h), who were excluded from further analysis, thus leading to a final population of 42 patients with and without CSA.

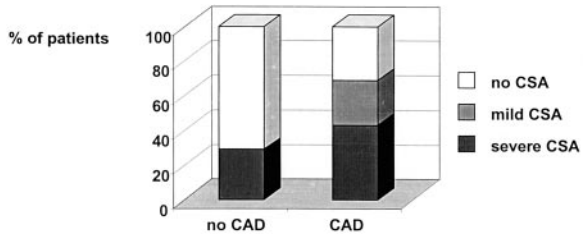

Figure 1. Prevalence of CSA according to the cause of cardiac disease. Patients with CAD showed a higher prevalence of CSA than patients without CAD.

History, demographics, physical examination findings, and nocturnal breathing data according to the diagnosis of CSA are presented in Figure 1 and Table 1. The prevalence and severity of CSA was higher in patients with ischemic cardiomyopathy compared with patients with nonischemic cardiomyopathy ($P<0.05$; Figure 1). Patients with severe CSA were older than patients without CSA ($P<0.05$; Table 1). A

TABLE 1. Clinical Data and Sleep Findings in Patients Without CSA and With Mild and Severe CSA

	No CSA (n=16)	Mild CSA (n=9)	Severe CSA (n=17)
Age, y	54±3	60±4	63±3†
Sex, F/M	2/14	3/6	0/17‡
Body mass index, kg/m^2	25.3±1.1	25.5±1.4	26.6±1.0
Heart rate, bpm	60±5	76±6*	58±6‡
Systolic pressure, mm Hg	118±6	116±7	123±7
Diastolic pressure, mm Hg	63±4	73±4	72±4
FEV1	91±6	93±7	88±5
FVC	94±6	91±6	90±5
FEV1/FVC	84±7	89±7	80±6
Medications, n			
Digoxin	8	4	9
ACE inhibitors	15	8	16
Diuretics	10	4	10
β-Blockers	7	2	8
Nitrates	8	5	9
Amiodarone	3	2	1
Sleep data			
AHI, n/h	7.0±1.6	22.8±2.2	41.5±1.6
Central index, n/h	6.5±1.5	22.5±2.0	40.9±1.5
Obstructive index, n/h	0±0.3	0.54±2.0	0.65±0.3
Cycle length, s	47.3±4.5	46.9±4.8	48.3±3.4
Blood gases	(n=6)	(n=6)	(n=6)
pH	7.43±0.01	7.44±0.01	7.43±0.02
Po_2, mm Hg	84±4	75±4	75±4
Pco_2, mm Hg	39±2	38±2	36±2
SaO_2, %	97±0.7	94±0.7	96±0.7

Values are mean±SEM or number of patients.

*$P<0.05$ between no CSA and mild CSA; †$P<0.05$ between no CSA and severe CSA; ‡$P<0.05$ between mild CSA and severe CSA.

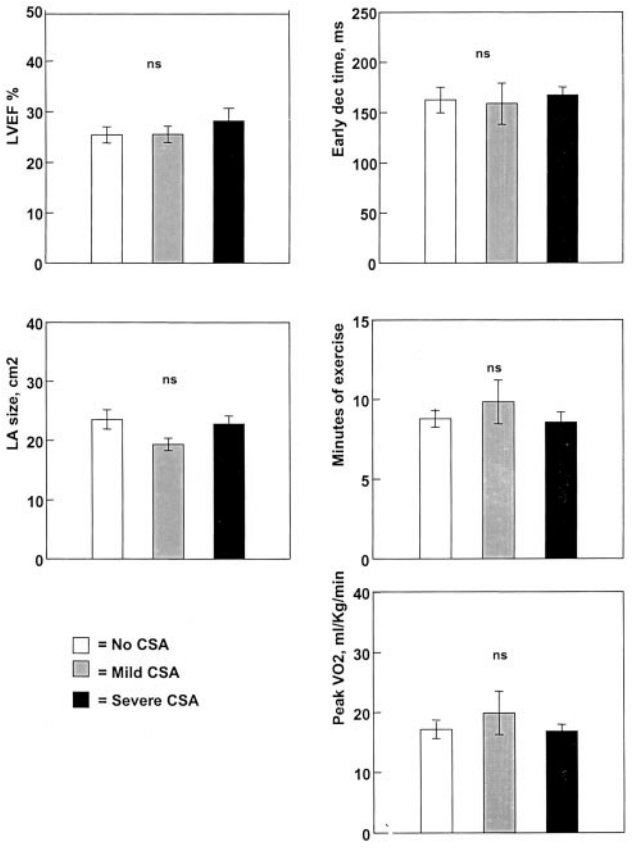

Figure 2. Hemodynamic and functional indices according to the presence and the severity of CSA. The patients without sleep apnea (no CSA) and with mild and severe CSA showed similar values of LV ejection fraction (LVEF), early deceleration (dec) time, left atrial (LA) size, minutes of exercise, and peak $\dot{V}O_2$.

higher resting heart rate was found in patients with mild CSA when compared with those without CSA and severe CSA ($P<0.05$). No differences were evident between all the groups in terms of body mass index, baseline arterial blood pressure, and medications.

The cycle-length was similar in the patients without CSA (9 of 16 patients with AHI<15/h had sequences of periodic breathing which made the measurement possible), with mild CSA, and with severe CSA (Table 1). Echocardiographic evaluation showed that the 3 groups of patients had similar indices of LV systolic and diastolic function and similar left atrial sizes (Figure 2).

Exercise tolerance and peak oxygen consumption ($\dot{V}O_2$) evaluations, which were obtained in 27 patients (64%), were also not different between the groups (Figure 2). Myocardial scintigraphy documented the presence of residual ischemia in 8 of the 35 patients with CAD (23%) and in 4 of the 15 patients with CAD and severe CSA (27%). The 24-hour Holter recordings were available in 39 of the 42 patients. Patients with both mild and severe CSA showed a significantly lower pNN50 than patients without CSA ($P<0.05$; Table 2 and Figure 3).

Patients with severe CSA tended to have a significantly higher occurrence of ventricular arrhythmias, as expressed by 24-hour premature ventricular contractions and day and nighttime premature ventricular contractions. Nonsustained ventricular tachycardias occurred almost exclusively in patients with severe CSA (Table 2 and Figure 3). Among severe CSA patients, those with residual ischemia did not show increased arrhythmias compared with those without ischemia: the number of premature ventricular contractions per hour was 21±76 in the ischemic group versus 125±48 in the nonischemic group (P=NS). Notably, only one patient with residual ischemia had ventricular tachycardia.

ANOVA did not show age, diabetes, cause of the disease, or history of CABG to influence the relationship between CSA and either the reduced heart rate variability or the increased ventricular arrhythmias.

TABLE 2. Twenty-Four-Hour ECG Data in Patients Without CSA and With Mild and Severe CSA

24-Hour ECG Data	No CSA (n=16)	Mild CSA (n=9)	Severe CSA (n=17)
Mean NN, ms	811±33	735±41	814±33
SdNN, ms	111±13	103±14	93±11
SDANN, ms	112±13	94±14	99±11
SD, ms	51±6	34±7	45±6
PNN50, %	11.3±2.4	0.9±2.9*	4.5±2.3†
24-Hour PVCs, n/h	51±50	15±66	141±47
Daytime PVCs, n/h	39±53	15±73	165±51
Nighttime PVCs, n/h	65±39	14±54	95±38
24-Hour NSVT	0.6±18	0.0±24	27±24
Daytime NSVT	1.1±21	0.1±29	33±21‡§
Nighttime NSVT	0.5±4	0.0±5	5.9±3.4

Values are given as mean±SEM. The 24-hour heart rate variability was quantified in the time domain: the mean normal-to-normal R-R interval (NN), the standard deviation of mean NN (sdNN), the standard deviation of all 5-minute mean RR intervals (SDANN), the mean of all 5-minute standard deviations of RR intervals (SD), and the percentage of >50 ms differences between adjacent NN (pNN50) were measured. PVC indicates premature ventricular contractions; NSVT, nonsustained ventricular tachycardia.

*$P<0.05$ between no CSA and mild CSA; †$P<0.05$ between no CSA and severe CSA; ‡$P<0.05$ between mild CSA and severe CSA; §$P=0.05$ between mild CSA and severe CSA.

Discussion

The novel findings in the present study are, first, that there is a very high prevalence of sleep-disordered breathing in patients with severe but asymptomatic LV dysfunction. The nature of the sleep-disordered breathing is primarily CSA, which was present in 55% of patients. Second, in contrast to patients with overt heart failure, there is no evidence of increased hemodynamic and functional compromise in patients with LV dysfunction and CSA. Indices such as LV ejection fraction, early deceleration time, exercise tolerance, and peak oxygen consumption are similar even in patients with the most severe CSA (AHI ≥30/h) compared with those with mild or absent CSA. Cycle-length, an index that may reflect hemodynamics and circulation time,[13] was similar in the patients without CSA and with mild and severe CSA. Nevertheless, there is impaired cardiac autonomic control and electrical instability in patients with severe CSA, as evi-

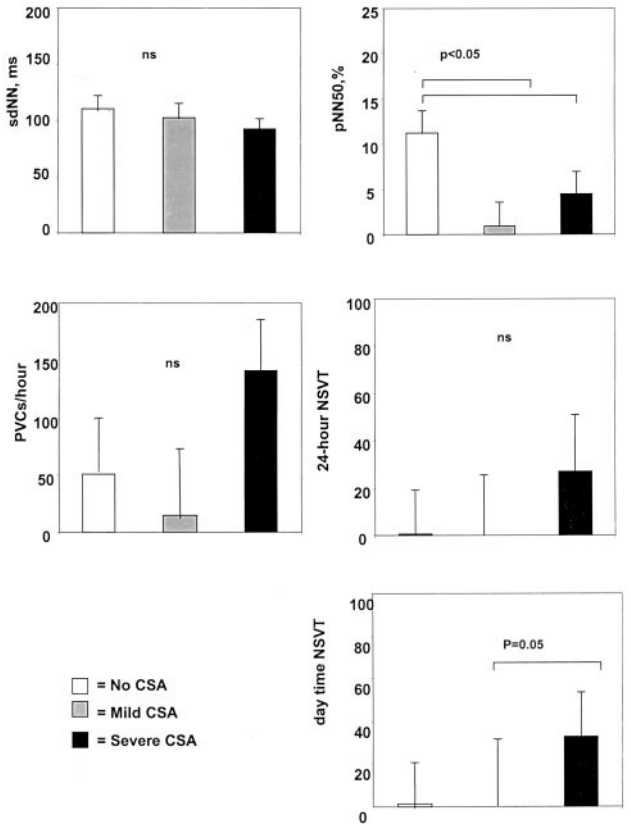

Figure 3. Heart rate variability and ventricular arrhythmias according to the presence and the severity of CSA. Patients with CSA had a significantly lower pNN50 than patients without CSA. Patients with severe CSA, when compared with those with absent or mild CSA, showed increased premature ventricular contractions (PVCs) and more frequent runs of nonsustained ventricular tachycardia (NSVT) in the daytime. sdNN indicates the standard deviation of mean NN.

denced by a dramatic reduction in pNN50 and increased ventricular arrhythmias.

Measurements of heart rate variability in the time domain provide objective assessments of abnormalities in neural circulatory control[11] and predict prognosis in post-myocardial infarction and heart failure patients.[14,15] Specifically, a diminished pNN50 is associated with increased runs of nonsustained ventricular tachycardia in patients with hypertrophic obstructive cardiomyopathy.[16] In patients with heart failure, lower pNN50 is an independent predictor of increased cardiac mortality.[17]

The pNN50 is a subtle indicator of cardiac autonomic control and is thought to reflect mainly the vagal component of cardiac regulation[11,18]; indeed, it is one of the earliest indicators of cardiac autonomic dysfunction. This has been demonstrated in patients with diabetes.[18,19] Also, patients with the earliest phases of Chaga's disease (when LV function is still normal) manifest abnormalities in pNN50, even though other measures of heart rate control are preserved.[20] Our present data show that in patients with asymptomatic LV dysfunction and CSA, pNN50 is reduced even in those with mild CSA.

Direct evidence of cardiac electrical instability in patients with severe CSA is apparent in the increased ventricular arrhythmias. Although CSA is especially prevalent in those patients with ischemic, compared with idiopathic LV dysfunction, the increased cardiac arrhythmias in patients with CSA does not seem to be a function of cardiac ischemia per se.

Javaheri et al[3] noted an association between sleep apnea and ventricular arrhythmias in patients with heart failure. Javaheri[21] subsequently observed that attenuation of sleep-disordered breathing by continuous positive airway pressure was accompanied by a significant reduction in ventricular arrhythmias, indicating a possible cause-effect relationship. We have extended these earlier observations in heart failure by demonstrating that patients with asymptomatic LV dysfunction also have a high prevalence of CSA, and that in these patients, severe CSA is associated with impairment in heart rate variability and increased cardiac arrhythmias.

In patients with overt heart failure, CSA correlated with pulmonary capillary wedge pressure, as measured by invasive[22] and noninvasive[23,24] approaches. In our present study of patients with LV dysfunction without overt heart failure, the presence and severity of CSA was not associated with increased ventricular impairment or hemodynamic indices of increased filling pressure (Figure 2). The presence and severity of sleep apnea also did not correlate with the ventilation-apnea length in our patients (Table 1). The cycle-length in our patients with severe CSA (48 s), although higher than the cycle-length reported in patients with idiopathic CSA and normal ventricular function (35 s),[13] is significantly lower than the cycle-length reported in patients with CSA and heart failure (69 s).[13,24] In our present study, the cycle-length was similar for all patients, thus confirming that the degree of hemodynamic dysfunction reflected by this index is equally present in these 3 groups and, therefore, is not the primary factor inducing CSA in our patients.

What would be the potential mechanisms for CSA in asymptomatic LV dysfunction? CSA is known to be strongly associated with heart failure or neurological lesions. Nevertheless, nocturnal periodic breathing with central apneas has also been recognized in healthy subjects,[25] indicating that it cannot be completely accounted for by either "cardiogenic" or "neurogenic" origins. It is currently believed that instability of respiration control may account for most of the observations of periodic breathing in disease, as well as in health.[26] Periodic breathing has been explained as a self-sustaining oscillation due to the loss of stability in the closed-loop chemical control of ventilation[26] due, in heart failure, to an enhanced loop gain (hyperventilation), a slow circulation time between lungs and chemoreceptors, and inability to adjust to perturbations in the blood gases.[24]

Heart failure patients with CSA–Cheyne-Stokes respiration (CSR) tend to hyperventilate.[27] This tendency to hyperventilate has been attributed in part to the afferent stimulation from pulmonary venous congestion.[22] However, CSA-CSR does not always occur in patients with severely compromised hemodynamic and pulmonary congestion.[28] Indeed, an enhanced ventilatory chemoreflex response to CO_2 may play a crucial role in the development of CSA-CSR in heart failure.[29] Although the chemoreflex was not evaluated in our study, our CSA patients showed a tendency to lower values of daytime P_{CO_2}.

Small lung volumes may contribute to ventilatory instability by impairing the capacity to buffer changes in blood gases during transient changes in ventilation. Total lung capacity was not measured in our study. However, in our patients with an AHI ≥15/h, FVC was 92% of predicted versus 82% to 86% reported in previous series of patients with CSA in the setting of heart failure.[13,27]

A delayed feedback control by a prolonged circulation time due to a reduced cardiac output is, in heart failure, a further factor promoting instability. The estimated circulation time (which is about one-third of the cycle-length)[13] in our subjects was slightly increased but significantly lower than the values shown in the literature for heart failure.[13,18] The small increments in circulation time we estimated would be unlikely to promote periodic breathing, unless concomitant with an increased chemosensitivity.[24]

Finally, impaired baroreflex control may also induce an instability in the control of ventilation. Baroreflex deactivation augments the ventilatory response to stimulation of the peripheral chemoreceptors.[30] Baroreflex control is disturbed in patients with even mild impairment of ventricular function,[31] possibly resulting in enhanced chemoreflex gain. Augmented peripheral chemosensitivity may contribute to periodic breathing in awake heart failure patients, as well as to CSA and to autonomic dysfunction.[32] Therefore, it is conceivable that chemoreflex-baroreflex interactions may be implicated in the genesis of abnormalities in breathing control leading to CSA in patients with LV dysfunction.

Limitations of the study include, first, that sleep monitoring was conducted using an unattended system. Nevertheless, this is a valid approach to monitoring cardiorespiratory function during sleep.[33] Second, patients were on drug therapy during these studies. In mitigation, an important objective of this study was to avoid interruption of the normal therapy. Furthermore, there was no difference in distribution of drug therapy in the different populations of apnea severity. A third limitation is that the CSA tended to be greater in older patients, which is consistent with findings in other studies.[34] However, analysis with age as a covariate did not indicate any interaction between age and apnea index in measurements of autonomic dysfunction or arrhythmias.

Conclusions

Patients with severe but asymptomatic LV dysfunction have a high prevalence of CSA. Severe CSA is associated with impaired cardiac autonomic control and increased cardiac arrhythmias but not with greater hemodynamic impairment. Patients with asymptomatic LV dysfunction are at risk for progression to overt heart failure and for sudden death, particularly in the setting of ischemic LV dysfunction. The high prevalence of severe CSA in patients with ischemic LV dysfunction and the association between severe CSA and both cardiac autonomic dysfunction and cardiac arrhythmias suggest that sleep-disordered breathing may be implicated in increased cardiovascular risk in patients with impaired LV function, even in the absence of overt heart failure.

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