Association of Smoking, Sleep Apnea, and Plasma Alkalosis With Nocturnal Ventricular Arrhythmias in Men With Systolic Heart Failure

Shahrokh Javaheri, MD, FCCP; Rakesh Shukla, PhD; and Laura Wexler, MD

Background: Excess sudden death due to ventricular tachyarrhythmias remains a major mode of mortality in patients with systolic heart failure. The aim of this study was to determine the association of nocturnal ventricular arrhythmias in patients with low ejection fraction heart failure. We incorporated a large number of known pathophysiologic triggers to identify potential targets for therapy to reduce the persistently high incidence of sudden death in this population despite contemporary treatment.

Methods: Eighty-six ambulatory male patients with stable low ($\leq 45\%$) ejection fraction heart failure underwent full-night attendant polysomnography and simultaneous Holter recordings. Patients were divided into groups according to the presence or absence of couplets (paired premature ventricular excitations) and ventricular tachycardia (VT) (at least three consecutive premature ventricular excitations) during sleep.

Results: In multiple regression analysis, four variables (current smoking status, increased number of arousals, plasma alkalinity, and old age) were associated with VT and two variables (apnea-hypopnea index and low right ventricular ejection fraction) were associated with couplets during sleep.

Conclusions: We speculate that cessation of smoking, effective treatment of sleep apnea, and plasma alkalosis could collectively decrease the incidence of nocturnal ventricular tachyarrhythmias and the consequent risk of sudden death, which remains high despite the use of β blockades.

CHEST 2012; 141(6):1449–1456

Abbreviations: AHI = apnea-hypopnea index; ArI = arousal index; CSA = central sleep apnea; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; VT = ventricular tachycardia

Systolic heart failure is a highly prevalent disorder, affecting an estimated 5 million patients in the United States; heart failure occurs in 500,000 to 600,000 new patients annually. Despite advances in pharmacologic therapy, mortality remains high, with sudden death presumably due to ventricular arrhythmias being a major mode.^{1,2} In the enalapril trial,³ better survival was mainly due to improved pump

failure, with little effect on the incidence of sudden death when enalapril was compared with placebo. Also in a β -blocker trial⁴ comparing carvedilol to metoprolol, during the follow-up period 218 of 512 (40%) deaths in the carvedilol group, and 264 of 600 (44%) deaths in the metoprolol group were due to sudden cardiac death.

Meanwhile, an estimated 20% of sudden deaths in patients with heart failure occur at night,² and there

Manuscript received July 9, 2011; revision accepted November 1, 2011.

Affiliations: From the Department of Internal Medicine (Drs Javaheri and Wexler), and the Departments of Medicine and Environmental Health (Dr Shukla), University of Cincinnati College of Medicine; and the Department of Veterans Affairs Medical Center (Drs Javaheri and Wexler), Cincinnati, OH.

Funding/Support: Dr Javaheri was supported by grants from the VA Merit Review Program.

Correspondence to: Shahrokh Javaheri, MD, FCCP, Sleepcare Diagnostics, 4780 Sociaville Fosters Rd, Mason, OH 45040; e-mail: javaheri@snorenomore.com

© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1378/chest.11-1724

are multiple reasons for vulnerability to arrhythmias while asleep.¹ One factor is that sleep apnea, which is common in patients with heart failure,⁵⁻⁹ is associated with excess mortality,⁹⁻¹² especially during sleep.¹³ This suggests that patients with systolic heart failure and with sleep apnea may be at a particularly high risk of ventricular arrhythmias during sleep and that this may contribute to the persistence of sudden death in this population of patients.

Although multiple studies have been published on nocturnal arrhythmias in patients with obstructive sleep apnea,¹⁴⁻¹⁸ studies in heart failure are limited. Initial studies^{19,20} using only pulse oximetry drew attention to the presence of arrhythmias during sleep, concluding that in patients with systolic heart failure, nocturnal oxyhemoglobin desaturation was potentially arrhythmogenic. The results of recent studies,^{7,21,22} although not all,²³ are confirmatory. Two important issues are applicable to virtually all previous studies. First, the studies did not consider other multiple risk factors that may trigger arrhythmias. Second, the studies used either oximetry or mostly polygraphy without the benefit of EEG, an important omission, because arousals, which are associated with sympathetic activity, could not be included in the analysis of the data.

In the current study, we incorporated 28 pathophysiologic variables, including polysomnographic variables, electrolytes, BP, and smoking status to determine the association with ventricular arrhythmias. With regard to the last, studies have shown that smoking is associated with sudden death, and in patients with heart disease cessation of smoking diminishes the risk.^{24,25} We found that three conditions common in patients with systolic heart failure (ie, smoking status, sleep apnea, and plasma alkalinity) predict nocturnal ventricular arrhythmias that may predispose such patients to sudden death during sleep. The novel findings were that among the three triggers smoking had the highest OR and has important implications for counseling.

MATERIALS AND METHODS

Patient Population

Our laboratory has been involved in a series of prospective studies^{6,12} of sleep apnea in patients with systolic heart failure (left ventricular ejection fraction [LVEF] $\leq 45\%$). Patients with stable chronic congestive heart failure were recruited from cardiology and primary care clinics. At the time of recruitment, no information was sought about symptoms or risks factors for sleep apnea. Each patient was evaluated to determine the cause of heart failure and to confirm that he was clinically stable, with no change in symptoms or hospitalization within the previous 4 weeks. Exclusion criteria were unstable angina; unstable heart failure; interstitial lung disease; obstructive lung defect; intrinsic renal and liver disorders; and use of morphine derivatives, benzodiaze-

pinines, or theophylline. Patients were admitted to the hospital for 2 consecutive days for polysomnography and laboratory tests (see next section). Patients refrained from drinking any caffeinated product during the period of hospitalization.

For uniformity, only male patients were studied because female patients are seldom referred to this center. This protocol was approved by the institutional review board of the University of Cincinnati Medical Center, approval number 90-3-2-2. Each patient signed the consent form.

One hundred of 114 eligible patients, (88% recruitment) agreed to participate. The main reasons for refusal were unwillingness to travel to or stay in the hospital for sleep studies. The mean LVEF of nine of the 14 nonparticipating patients in whom data were available was $18\% \pm 6\%$, which is similar to that of the participants in the study. One hundred patients underwent polysomnography, and all had Holter recording. In 14 patients the recording was technically poor and unreadable. Therefore, a total of 86 patients were involved in the study. At the time of the study, 71 patients were on an angiotensin-converting enzyme inhibitor, six were on hydralazine, 26 were on isosorbide dinitrate, 71 were on a diuretic, 68 were on digoxin, and 10 were on a β -blocker.

Study Protocol

The patients were admitted to the hospital for two consecutive nights of attended polysomnography. On the first night, the patients slept in the sleep laboratory, and electrodes were placed for habituation to the environment of the laboratory. Caffeinated products were proscribed. A detailed history including sleep habits was obtained, and a physical examination was performed by one author (S. J.). The following tests were also obtained within the period of hospitalization: CBC count, serum electrolytes, blood urea nitrogen, serum creatinine, digoxin level, radionuclide ventriculography, arterial blood gases and pH, and pulmonary function tests. Details have been published previously.⁶

Polysomnography

On the second night, polysomnography was performed using standard techniques as detailed previously.⁶ We recorded EEG, electrooculogram, and chin electromyogram. Thoracoabdominal excursions (respiratory inductive plethysmography) and naso-oral airflow (using a thermocouple) were measured qualitatively, and arterial blood oxyhemoglobin saturation was recorded using a pulse oximeter. These variables were recorded on a multichannel polygraph (Model 78D; Grass Technologies).

Standard definitions were used for sleep-related disordered breathing. An apnea was defined as cessation of inspiratory airflow for 10 s or more. An obstructive apnea was defined as the absence of airflow in the presence of rib cage and abdominal excursions. A central apnea was defined as the absence of rib cage and abdominal excursions with the absence of airflow. Hypopnea was defined as a discernible reduction (30%) of airflow or thoracoabdominal excursions lasting 10 s or more associated with at least a 4% drop in arterial oxyhemoglobin saturation and/or an arousal. Hypopneas were classified obstructive if thoracoabdominal excursions were out of phase. The number of apneas and hypopneas per hour of sleep is referred to as the apnea-hypopnea index (AHI). An arousal was defined as the appearance of α waves on EEG for at least 3 s,²⁶ the number of arousals per hour of sleep is the arousal index (ArI), and the number of arousals associated with a disordered breathing episode per hour of sleep is the disordered breathing ArI. Polysomnograms were scored blindly by one of the authors (S. J.).

Holter Recording

Holter recording was done during polysomnography. Three ECG channels (leads V_1 , V_3 , and V_5) were recorded using a Laser

SxP Holter recording system (Marquette Electronics Inc). The tapes were analyzed by computer and were manually overread by the cardiologist coinvestigator (L. W.).

Statistical Analysis

The primary outcome variables were number of nocturnal couplets (1 $\geq$ per hour in bed) and ventricular tachycardias (VTs) (three premature ventricular contractions in a row, $\geq$ 1 per hour in bed). We dichotomized these variables using the specified cutoff points because in our previous study²⁷ we found an association between these arrhythmia thresholds and sleep apnea.

To assess the effect of independent variables on these two outcome variables, we included 28 potential candidate variables. These included age; BMI; heart rate; absolute BP and the difference between systolic BP and diastolic BP; smoking status; New York Heart Association functional class; cause of heart failure (ischemic vs idiopathic cardiomyopathy); right ventricular ejection fraction (RVEF) and LVEF; hemoglobin, hematocrit, serum [Na⁺], [K⁺], and digoxin levels; arterial plasma [H⁺]; [HCO₃⁻]; PaO₂; and PaCO₂. Sleep-related breathing disorder events included in the analysis were AHI, obstructive AHI, central AHI, baseline supine oxyhemoglobin saturation before falling asleep, lowest oxygen saturation, time spent below oxygen saturation of 90% during sleep, ArI, and disordered breathing ArI.

A two-sample *t* test was used to obtain significant associations between continuous predictors and two dichotomized outcome variables separately. A χ^2 test was used to ascertain significant associations between outcome variables and categorical predictors. Multiple logistic regression analyses were performed to determine which potential predictors had significant effects on each of the outcome variables by controlling for other significant predictors. Only significant predictors (*P* < .10) identified in the univariate analysis were included in the starting model for the multivariate analyses. A backward elimination procedure was used to identify the final reduced model for each outcome. All identified variables were included in the model, and nonsignificant covariates were removed using a backward elimination procedure according to a selection stay criterion of *P* $\leq$.05. The OR and its 95% CI for each of the outcome variables were used to assess the importance of the covariates individually and independently. Data were analyzed with SAS software for Windows, version 8 (SAS Institute).

RESULTS

Among 86 patients, 42 had an AHI < 15/h, 36 had predominantly central sleep apnea (CSA) with an AHI $\geq$ 15/h, and eight had predominantly obstructive sleep apnea with an AHI $\geq$ 15/h. Descriptive statistics of patients with and without ventricular arrhythmias are presented in Tables 1 and 2. Patients with couplets had higher AHI, ArI, disordered breathing ArI, and heart rate and lower RVEF, LVEF, [H⁺], and hemoglobin compared with patients without couplets. A higher percentage of patients with couplets were smokers. Patients with VT during sleep had higher ArI and disordered breathing ArI and lower oxyhemoglobin saturation during sleep than did patients without VT. In addition, patients with VT were older and had lower plasma [H⁺] than did patients without VT.

Independent associations of variables with ventricular arrhythmias were derived from multiple logistic

Table 1—Potential Predictors of Couplets in Patients With Heart Failure

Variable	Without Couplets	With Couplets	<i>P</i> Value
Patients, No.	25	62	...
Age, y	62 $\pm$ 11	66 $\pm$ 10	.20
BMI, kg/m ²	29 $\pm$ 6	28 $\pm$ 6	1.0
HR, beats/min	75 $\pm$ 13	81 $\pm$ 13	.10
SBP-DBP, mm Hg	53 $\pm$ 18	50 $\pm$ 17	.50
Smoking			
Nonsmoker or ex-smoker	18	54	.10
Current smoker	7	8	...
NYHA functional class			
Class I, II	19	41	.4*
Class III	6	21	
RVEF, %	52 $\pm$ 11	44 $\pm$ 14	.01
LVEF, %	27 $\pm$ 10	23 $\pm$ 7	.05
AHI, No./h	12 $\pm$ 14	33 $\pm$ 26	.0003
ArI, No./h	19 $\pm$ 11	27 $\pm$ 22	.03
DBArI, No./h	6 $\pm$ 7	15 $\pm$ 15	.0003
Baseline SaO ₂ , %	95 $\pm$ 2	95 $\pm$ 2	.80
Lowest SaO ₂ , %	85 $\pm$ 8	81 $\pm$ 11	.10
Time below SaO ₂ of 90%, % TST	17 $\pm$ 40	32 $\pm$ 46	.20
PaO ₂ , mm Hg	81 $\pm$ 11	83 $\pm$ 11	.70
PaCO ₂ , mm Hg	39 $\pm$ 4	38 $\pm$ 5	.20
[H ⁺], nM	37 $\pm$ 1	36 $\pm$ 3	.02
[HCO ₃ ⁻], mM	28 $\pm$ 3	28 $\pm$ 4	.80
Hemoglobin, g %	15 $\pm$ 1	14 $\pm$ 2	.10
Hematocrit, %	44 $\pm$ 4	42 $\pm$ 5	.20
Na ⁺ , mM	139 $\pm$ 3	140 $\pm$ 3	.70
K ⁺ , mM	4 $\pm$ 0.4	4 $\pm$ 0.4	.50
Digoxin level, nM	0.6 $\pm$ 0.5	0.7 $\pm$ 0.6	.40
Cause of HF			
Ischemic	15	42	.60
Idiopathic	6	12	...

AHI = apnea-hypopnea index; ArI = arousal index; DBArI = disordered breathing arousal index; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction; SaO₂ = saturation measured by pulse oximetry during polysomnography in relaxed wakefulness; SBP-DBP = systolic – diastolic BP; TST = total sleep time.

**P* value given is for Class I and II vs Class III.

regression analysis (Table 3). Two variables (AHI and RVEF) were significantly associated with couplets during sleep. Patients with a higher AHI and a lower RVEF had a significantly higher risk of having couplets during sleep.

Four variables (smoking status, ArI, [H⁺], and age) were significantly associated with VT during sleep. Patients with a higher ArI and lower plasma [H⁺], those who were smokers, and those who were older were at significantly increased risk of having VT.

DISCUSSION

To our knowledge, this is the first study to use full-night polysomnography, concurrent Holter monitoring, and a large number of clinically relevant variables to

Table 2—Potential Predictors of Ventricular Tachycardia During Sleep in Patients With Heart Failure

Variable	Without VT	With VT	P Value
Patients, No.	54	33	...
Age, y	63 ± 10	67 ± 9	.05
BMI, kg/m ²	28 ± 6	28 ± 5	.70
HR, beats/min	79 ± 13	79 ± 12	.80
SBP-DBP, mm Hg	50 ± 15	53 ± 20	.40
Smoking			
Nonsmoker or ex-smoker	48	24	
Current smoker	6	9	.05 ^a
NYHA functional class %			
Class I, II	37	23	.10 ^b
Class III	17	10	
RVEF, %	48 ± 14	44 ± 13	.20
LVEF, %	25 ± 9	22 ± 7	.10
AHI, No./h	24 ± 23	31 ± 27	.20
ArI, No./h	19.7 ± 17.4	33.4 ± 20	.001
DBArI, No./h	9 ± 10	18 ± 17	.01
Baseline SaO ₂ , %	95 ± 2	95 ± 2	1.00
Lowest SaO ₂ , %	85 ± 8	79 ± 13	.02
Time below SaO ₂ of 90%, % TST	23 ± 44	35 ± 45	.30
PaO ₂ , mm Hg	83 ± 12	82 ± 9	.70
PaCO ₂ , mm Hg	39 ± 4	38 ± 5	.20
[H ⁺], nM	37 ± 2	36 ± 3	.045
[HCO ₃ ⁻], mM	28 ± 3	28 ± 4	.10
Hemoglobin, g %	14 ± 2	14 ± 2	1.00
Hematocrit, %	43 ± 5	43 ± 5	.90
Na ⁺ , mM	139 ± 3.2	140 ± 2.6	.18
K ⁺ , mM	4 ± 0.4	4 ± 0.4	.80
Digoxin level, nM	0.7 ± 0.6	0.7 ± 0.6	.80
Cause of HF			
Ischemic	33	24	.30
Idiopathic	13	5	...

VT = ventricular tachycardia. See Table 1 legend for expansion of other abbreviations.

^aP value given is for current smoker vs nonsmoker or ex-smoker.

^bP value given is for Class I and II vs Class III.

determine their association with nocturnal ventricular arrhythmias in patients with systolic heart failure. Among multiple pathophysiologic factors considered, three variables emerged as independently associated with nocturnal ventricular arrhythmias: current smok-

Table 3—Multiple Logistic Regression for Ventricular Arrhythmias During Sleep in Patients With Heart Failure

Variable	OR	95% CI	P Value
Patients with couplets vs patients without couplets			
AHI, No./h	1.05	1.01-1.08	.004
RVEF, %	0.94	0.9-0.99	.03
Patients with VT vs patients without VT			
ArI, No./h	1.05	1.02-1.08	.001
[H ⁺], nM	0.8	0.64-0.99	.04
Age, y	1.1	1.03-1.19	.008
Smoking status	9.96	1.93-51.48	.006

See Table 1 and 2 legends for expansion of other abbreviations.

ing status, specific parameters of sleep-disordered breathing, and plasma alkalinity.

The patients with couplets had a significantly higher AHI (33/h vs 12/h, $P = .0003$), ArI (27/h vs 19/h, $P = .026$), and disordered breathing ArI (15/h vs 6/h, $P = .0003$) compared with those without couplets. Furthermore, in multiple regression analysis, a high AHI and low RVEF were independently associated with the presence of couplets during sleep.

Approximately 40% of the patients with systolic heart failure had VT while asleep and they exhibited lower arterial oxyhemoglobin saturation (79% vs 85%, $P = .02$) and a higher number of arousals (33/h vs 20/h, $P = .001$) and ArI related to sleep-disordered breathing events (18/h vs 9/h, $P = .002$) compared with patients without VT. In multiple regression analysis, current smoking history, a higher ArI during sleep, lower plasma hydrogen ion concentration, and older age, were independently associated with the presence of VT (Table 3).

The pathogenesis of ventricular arrhythmias in systolic heart failure has yet to be fully elucidated and remains a topic of critical importance given the persistently high rate of sudden death in these patients despite advances in therapy with β -blockers.^{4,28,29} Therefore, identifying any residual risk factors that may contribute to persistent sudden cardiac death, particularly if the risk factors are treatable, is of therapeutic importance. The remainder of our discussion relates to the three treatable risk factors, sleep apnea, smoking, and alkalemia, which we found to be independent predictors of ventricular instability during sleep.

Sleep Apnea

We report that two specific measures of sleep-disordered breathing, AHI and ArI, are independently associated with the presence of couplets and VT, respectively, in patients with systolic heart failure. AHI, one of the defining measures of sleep apnea and its severity, reflects the composite of altered blood gas chemistry, arousals, and changes in intrathoracic pressure, all of which could contribute to the development of ventricular arrhythmias or to the perpetuation of such arrhythmias in patients already susceptible to malignant arrhythmias by virtue of their myocardial pathology.

Prior studies³⁰⁻³³ have shown an association between sleep apnea, both obstructive and central, and increased sympathetic activity. Furthermore, it has been shown that treatment of both kinds of sleep apnea with CPAP devices decreases sympathetic activity^{31,32} and the frequency of ventricular arrhythmias.^{34,35} Collectively, these studies strongly indicate that both obstructive and central sleep apnea create a hyperadrenergic state and a substrate for ventricular irritability. The

two major consequences of sleep apnea that are directly related to sympathetic hyperactivity are CNS arousals^{36,37} and altered blood gas chemistry.³⁸ However, independent of increased sympathetic activity, sleep apnea-related hypoxemia, which may result in decreased myocardial oxygen delivery, and the negative swings in intrathoracic pressure associated with the apnea-recovery cycle (which increases left ventricular afterload) may also result in an imbalance between myocardial oxygen supply and demand, causing myocardial ischemia, which is arrhythmogenic. The latter two mechanisms and the imbalance of myocardial delivery and demand of oxygen are particularly critical because during sleep diastolic BP, the major determinant of coronary blood flow, decreases, resulting in a further drop in coronary blood flow, a condition referred to as nondemand ischemia.¹ In this context, in a previous study,¹² we found that in patients with heart failure, low diastolic BP is a predictor of mortality.

The results of our study linking parameters of sleep apnea to arrhythmias during sleep are consistent with the findings of two other recent studies,^{21,22} in which >80% of the patients were on a β -blocker.

Smoking

The novel, and the most important, finding of the present study is that current smoking in patients with systolic heart failure is associated with VT with an OR of about 10. Smoking by production of carboxyhemoglobin, and via mechanisms mediated by nicotine, causes coronary vasospasm,³⁹ which, along with apnea-related desaturation, can result in myocardial ischemia, which is arrhythmogenic. Furthermore, nicotine increases efferent sympathetic activity (at least in part because of stimulating peripheral chemoreceptors in the carotid bodies, which contain excitatory nicotinic receptors) and plasma catecholamine, resulting in increases in BP, heart rate, and myocardial oxygen consumption, which, along with decreases in oxygen availability and coronary vasospasm, collectively result in a supply-demand imbalance and promote ventricular tachyarrhythmias.^{24,25}

Our results are consistent with those of studies that suggest that cigarette smoking is associated with a significant increase in the risk of life-threatening ventricular tachyarrhythmias and sudden death^{24,25} and increased mortality of patients with left ventricular systolic dysfunction.⁴⁰ Importantly, however, in our cohort of systolic heart failure and sleep apnea, exposure to smoking was associated with an elevated risk of arrhythmias, with an OR of 10, far above the OR (of about 2) reported in previous studies.^{24,25,40} This may be related to similarities between the adverse pathophysiologic consequences of smoking and sleep

apnea on the cardiovascular system. This finding has important implications for clinical practice, emphasizing the role of counseling and the use of other measures for cessation of smoking in patients with systolic heart failure and sleep apnea because it may be a significant factor in promoting ventricular irritability and sudden cardiac death. And, importantly, smoking cessation is associated with a reduced risk of sudden cardiac death in patients with coronary artery disease²⁵ and systolic heart failure.⁴¹

Alkalosis

We believe we are the first to report that a low steady-state plasma hydrogen ion concentration (due to either respiratory or metabolic alkaloses, which are common in patients with heart failure because of chronic hyperventilation and use of diuretics) is associated with ventricular tachyarrhythmias. Alkalemia is known to induce ventricular irritability,^{42,43} which may be caused, at least in part, by increased sympathetic activity,⁴⁴⁻⁴⁷ similar to the proposed mechanisms of sleep apnea and nicotine-associated dysrhythmias.

The results of the present study are consistent with those of our previous study,⁴⁸ showing that a low PCO_2 was a predictor of ventricular irritability in heart failure patients; the present study, involving a larger number of patients, indicates that it is a low hydrogen ion concentration, not necessarily a low PCO_2 , that is associated with ventricular irritability.

Regarding alkalemia, two important points are emphasized. First, the pathogenic mechanism of alkalemia as a cause of arrhythmia is most relevant in conjunction with sleep-related breathing disorders, because alkalemia is further augmented when hyperventilation follows the cycles of apnea and PCO_2 is lowered. Second, alkalemia, by decreasing PCO_2 reserve below eupnea, increases the likelihood of periodic breathing,⁴⁹ resulting in a vicious cycle.

Some of the limitations of this study need to be acknowledged. At the time the data were collected, almost all patients were on an angiotensin-converting enzyme inhibitor but only a minority were on β -blocker therapy. In this context, two important points are emphasized. First, our results are most applicable to the significant number of heart failure patients who either cannot or will not take β -blockers because they are intolerant or not compliant or have contraindications to therapy. The percentage of such patients varies, depending on the nature of the studies. When recruited for a recent research study,⁵⁰ about 15% of the 2,737 patients with heart failure were not on a β -blocker. Furthermore, despite the recent guidelines, the percentage increases considerably in patients followed in clinical practices. Thirty-two percent in one study⁵¹ and 63% in another⁵² were not on a

β -blocker. Second, as noted before, our results are consistent with those of studies^{21,22} in which > 80% of patients were on β -blockers. Collectively, the results of these two studies along with ours suggest that in the face of sleep apnea, administration of β -blockers does not adequately diminish the vulnerability to arrhythmias. This could be due in part to multiple apnea-related consequences, including diminished myocardial oxygen delivery due to hypoxia and changes in intrathoracic pressure, which may trigger arrhythmias independent of sympathetic activity and the presence of β -blockers. Another limitation of our study is the small number of patients with obstructive sleep apnea (eight of 86) or CSA (36 of 86), for which reason we were unable to statistically determine the independent effect of disordered breathing on arrhythmias in a multivariable settings. However, we emphasize that the nocturnal consequences of both obstructive sleep apnea and CSA are qualitatively similar and, as shown by Bitter et al,²² both disorders predict arrhythmias. Also, over the short and long term, a shift in sleep apnea types occurs because of changes in position, circulation time,⁵³ and fluid shifts.⁵⁴

CONCLUSIONS

In conclusion, although ventricular arrhythmias are generally suppressed during sleep,^{1,4,55} patients with heart failure have persistence of arrhythmias at night, and sudden cardiac death accounts for a large number of deaths. The present study shows that smoking, some of the parameters of sleep apnea, and alkalemia are significantly associated with ventricular couplets and VT during sleep, and we hypothesize this may be related to the observation of excess nocturnal mortality in systolic heart failure. We speculate that specific therapy aimed at smoking cessation, reversal of alkalemia, and treatment of sleep apnea might further reduce the mortality rate in systolic heart failure.

ACKNOWLEDGMENTS

Author contributions: Dr Javaheri: contributed to all aspects of the study.

Dr Shukla: contributed to the analysis of the data and related discussions.

Dr Wexler: contributed to the recruitment and examination of the patients, concept development, and writing of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Javaheri has received honoraria for lectures from Philips Respironics and ResMed, which included expenses for travel and honoraria for presentations. He has performed research for Philips Respironics and received grants from them for patient enrollment in the study. He is a consultant to Respcardia Inc (a company making a phrenic nerve stimulation device) and to Sova Pharmaceuticals Inc and Cortex Pharmaceuticals Inc, pharmaceutical companies

making drugs for central sleep apnea. Dr Wexler is a paid contributor to the online textbook UpToDate. Dr Shukla has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Other contributions: We acknowledge the expert statistical help of H. Zeigler, MS, and the editorial assistance of N. Harris, RPSGT.

REFERENCES

- Verrier RL, Josephson ME. Impact of sleep on arrhythmogenesis. *Circ Arrhythm Electrophysiol*. 2009;2(4):450-459.
- Carson PA, O'Connor CM, Miller AB, et al. Circadian rhythm and sudden death in heart failure: results from Prospective Randomized Amlodipine Survival Trial. *J Am Coll Cardiol*. 2000;36(2):541-546.
- Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med*. 1991; 325(5):293-302.
- Poole-Wilson PA, Swedberg K, Cleland JGF, et al; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003;362(9377):7-13.
- Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease. An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*. 2008;118(10):1080-1111.
- Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation*. 1998;97(21):2154-2159.
- Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. *Circulation*. 2003;107(5):727-732.
- Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Töpfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail*. 2007; 9(3):251-257.
- Arzt M, Floras JS, Logan AG, et al; CANPAP Investigators. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation*. 2007;115(25): 3173-3180.
- Corrà U, Pistono M, Mezzani A, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation*. 2006;113(1):44-50.
- Lanfranchi PA, Braghiroli A, Bosimini E, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation*. 1999;99(11):1435-1440.
- Javaheri S, Shukla R, Zeigler H, Wexler LF. Central sleep apnea, right ventricular dysfunction, and low diastolic blood

- pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol*. 2007;49(20):2028-2034.
13. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352(12):1206-1214.
 14. Mehra R, Benjamin EJ, Shahar E, et al; Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2006;173(8):910-916.
 15. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol*. 1983;52(5):490-494.
 16. Alonso-Fernández A, García-Río F, Racionero MA, et al. Cardiac rhythm disturbances and ST-segment depression episodes in patients with obstructive sleep apnea-hypopnea syndrome and its mechanisms. *Chest*. 2005;127(1):15-22.
 17. Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. Prevalence and significance. *Am J Med*. 1982;73(3):317-321.
 18. Monahan K, Storfer-Isser A, Mehra R, et al. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. *J Am Coll Cardiol*. 2009;54(19):1797-1804.
 19. Davies SW, John LM, Wedzicha JA, Lipkin DP. Overnight studies in severe chronic left heart failure: arrhythmias and oxygen desaturation. *Br Heart J*. 1991;65(2):77-83.
 20. Cripps T, Rucker G, Stradling J. Nocturnal hypoxia and arrhythmias in patients with impaired left ventricular function. *Br Heart J*. 1992;68(4):382-386.
 21. Serizawa N, Yumino D, Kajimoto K, et al. Impact of sleep-disordered breathing on life-threatening ventricular arrhythmia in heart failure patients with implantable cardioverter-defibrillator. *Am J Cardiol*. 2008;102(8):1064-1068.
 22. Bitter T, Westerheide N, Prinz C, et al. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. *Eur Heart J*. 2011;32(1):61-74.
 23. Staniforth AD, Sporton SC, Early MJ, Wedzicha JA, Nathan AW, Schilling RJ. Ventricular arrhythmia, Cheyne-Stokes respiration, and death: observations from patients with defibrillators. *Heart*. 2005;91(11):1418-1422.
 24. Goldenberg I, Moss AJ, McNitt S, et al; Multicenter Automatic Defibrillator Implantation Trial-II Investigators. Cigarette smoking and the risk of supraventricular and ventricular tachyarrhythmias in high-risk cardiac patients with implantable cardioverter defibrillators. *J Cardiovasc Electrophysiol*. 2006;17(9):931-936.
 25. Goldenberg I, Jonas M, Tenenbaum A, et al; Bezafibrate Infarction Prevention Study Group. Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. *Arch Intern Med*. 2003;163(19):2301-2305.
 26. Bonnet M, Carley D, Carskadon M, et al. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep*. 1992;15(2):174-184.
 27. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. *Int J Cardiol*. 2006;106(1):21-28.
 28. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-2007.
 29. Packer M, Coats AJ, Fowler MB, et al; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344(22):1651-1658.
 30. van de Borne P, Oren R, Abouassaly C, Anderson E, Somers VK. Effect of Cheyne-Stokes respiration on muscle sympathetic nerve activity in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1998;81(4):432-436.
 31. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med*. 1995;152(2):473-479.
 32. Usui K, Bradley TD, Spaak J, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. *J Am Coll Cardiol*. 2005;45(12):2008-2011.
 33. Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation*. 1998;98(8):772-776.
 34. Javaheri S. Effect of continuous positive airway pressure of sleep apnea and ventricular irritability in patients with heart failure. *Circulation*. 2000;101(4):391-397.
 35. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. *Thorax*. 2005;60(9):781-785.
 36. Morgan BJ, Crabtree DC, Puleo DS, Badr MS, Toiber F, Skatrud JB. Neurocirculatory consequences of abrupt change in sleep state in humans. *J Appl Physiol*. 1996;80(5):1627-1636.
 37. Schneider H, Schaub CD, Chen CA, et al. Effects of arousal and sleep state on systemic and pulmonary hemodynamics in obstructive apnea. *J Appl Physiol*. 2000;88(3):1084-1092.
 38. Somers VK, Mark AL, Zavala DC, Abboud FM. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol*. 1989;67(5):2101-2106.
 39. Sugishima M, Takatsu F. Cigarette smoking is a major risk factor for coronary spasm. *Circulation*. 1993;87(1):76-79.
 40. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2001;37(6):1677-1682.
 41. Peters RW, Brooks MM, Todd L, Liebson PR, Wilhelmsen L; The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Smoking cessation and arrhythmic death: the CAST experience. *J Am Coll Cardiol*. 1995;26(5):1287-1292.
 42. Ayres SM, Grace WJ. Inappropriate ventilation and hypoxemia as causes of cardiac arrhythmias. The control of arrhythmias without antiarrhythmic drugs. *Am J Med*. 1969;46(4):495-505.
 43. Gennari FJ, Kassirer JP. Respiratory alkalosis. In: Cohen JJ, Kassirer JP, eds. *Acid-Base*. Boston, MA: Little, Brown; 1982: 349-376.
 44. Somers VK, Mark AL, Zavala DC, Abboud FM. Influence of ventilation and hypocapnia on sympathetic nerve responses to hypoxia in normal humans. *J Appl Physiol*. 1989;67(5):2095-2100.
 45. Stäubli M, Rohner F, Kammer P, Ziegler W, Straub PW. Plasma volume and proteins in voluntary hyperventilation. *J Appl Physiol*. 1986;60(5):1549-1553.
 46. Krapf R, Caduff P, Wagdi P, Stäubli M, Hulter HN. Plasma potassium response to acute respiratory alkalosis. *Kidney Int*. 1995;47(1):217-224.
 47. Mitchell JH, Wildenthal K, Johnson RL Jr. The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney Int*. 1972;1(5):375-389.
 48. Javaheri S, Corbett WS. Association of low PaCO₂ with central sleep apnea and ventricular arrhythmias in ambulatory

- patients with stable heart failure. *Ann Intern Med.* 1998; 128(3):204-207.
49. Nakayama H, Smith CA, Rodman JR, Skatrud JB, Dempsey JS. Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. *Am J Respir Crit Care Med.* 2002; 165(9):1251-1260.
 50. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Eng J Med.* 2011;364(1):11-21.
 51. Dahlstrom U, Hakansson J, Swedberg K, Waldenstrom A. Adequacy of diagnosis and treatment of chronic heart failure in primary health care in Sweden. *Eur J Heart Fail.* 2009; 11(1):92-98.
 52. Calvert MJ, Shankar A, McManus RJ, Ryan R, Freemantle N. Evaluation of the management of heart failure in primary care. *Fam Pract.* 2009;26(2):145-153.
 53. Ryan CM, Floras JS, Logan AG, et al; CANPAP Investigators. Shift in sleep apnoea type in heart failure patients in the CANPAP trial. *Eur Respir J.* 2010;35(3):592-597.
 54. Chiu K-L, Ryan CM, Shiota S, et al. Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. *Am J Respir Crit Care Med.* 2006;174(12):1378-1383.
 55. Verrier RL, Mittleman MA. Sleep-related cardiac risk. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia, PA: Elsevier; 2010:1161-1170.