Published in final edited form as:

Sleep Breath. 2011 December ; 15(4): 827–835. doi:10.1007/s11325-010-0444-2.

Predictors of oxidative stress in heart failure patients with Cheyne–Stokes respiration

Ana C. Krieger,

Weill Cornell Medical College of Cornell University, 425 East 61th Street – 5th floor, New York, NY 10065, USA

Daniel Green,

North Shore University Hospital, Manhasset, NY, USA

Muriel T. Cruz,

VA New York Harbor Health Care System, New York, NY, USA

Frank Modersitzki,

New York University School of Medicine, New York, NY, USA

Gita Yitta,

University of Pennsylvania School of Dental Medicine, Philadelphia, PA, USA

Sanja Jelic,

Columbia University College of Physicians and Surgeons, New York, NY, USA

Doris S. Tse, and

New York University School of Medicine, New York, NY, USA

Steven P. Sedlis

VA New York Harbor Health Care System, New York, NY, USA; New York University School of Medicine, New York, NY, USA

Abstract

Purpose—Cheyne–Stokes respiration during sleep is associated with increased mortality in heart failure. The magnitude of oxidative stress is a marker of disease severity and a valuable predictor of mortality in heart failure. Increased oxidative stress associated with periodic breathing during Cheyne–Stokes respiration may mediate increased mortality in these patients. We hypothesized that the presence of Cheyne–Stokes respiration is associated with oxidative stress by increasing the formation of reactive oxygen species in patients with heart failure.

Methods and results—Twenty-three patients with heart failure [left ventricular ejection fraction $30.2 \pm 9\%$ (mean $\pm$ standard deviation)] and 11 healthy controls underwent nocturnal polysomnography. Subjects with obstructive sleep apnea were excluded. The majority (88%) of patients with heart failure had Cheyne–Stokes respiration during sleep. The intensity of oxidative stress in neutrophils was greater in patients with heart failure ($4,218 \pm 1,706$ mean fluorescence

Correspondence to: Ana C. Krieger.

Conflict of interest: None of the authors has a conflict of interest to disclose.

intensity/cell vs. $1,003 \pm 348$ for controls, $p < 0.001$) and correlated with the duration of Cheyne–Stokes respiration. Oxidative stress was negatively correlated with SaO_2 nadir during sleep ($r = -0.43$, $p = 0.039$). The duration of Cheyne–Stokes respiration predicted severity of oxidative stress in patients with heart failure (beta = 483 mean fluorescence intensity/cell, $p < 0.02$).

Conclusions—Levels of oxidative stress are increased in patients with heart failure and Cheyne–Stokes respiration during sleep compared with healthy controls. The duration of Cheyne–Stokes respiration predicts the magnitude of oxidative stress in heart failure. Increased oxidative stress may mediate increased mortality associated with Cheyne–Stokes respiration in patients with heart failure.

Keywords

Oxidative stress; Heart failure; Cheyne-stokes respiration; Periodic breathing; Hypoxemia; Sleep apnea

Cheyne–Stokes respiration, the predominant form of sleep-related respiratory disturbance in patients with heart failure, is characterized by alternating periods of crescendo and decrescendo respiration followed by central apneas [1–5]. Unlike obstructive sleep apnea, which occurs due to airway obstruction, Cheyne–Stokes respiration is caused by oscillations in central respiratory control. Little is known about the effects of altered central respiratory control on cellular oxidative stress. Cheyne–Stokes respiration during sleep is associated with increased mortality among patients with heart failure when compared to heart failure patients without Cheyne–Stokes respiration, independent of left ventricular function [6–11]. However, the mechanisms linking Cheyne–Stokes respiration during sleep to increased mortality in heart failure are unknown. We hypothesized that intermittent hypoxemia periods associated with transient cessation of breathing during Cheyne–Stokes respiration increase cellular oxidative stress resulting in progression of myocardial failure and, ultimately, cell death. We compared the levels of oxidative stress in neutrophils of heart failure patients with Cheyne–Stokes respiration during sleep and healthy controls.

Materials and methods

Study sample

Adult male patients with stable heart failure and New York Heart Association (NYHA) class 2 were recruited from the Cardiology Clinic at the VA New York Harbor Healthcare System. All participants signed an informed consent approved by the Institutional Review Board. The inclusion criteria for the heart failure subjects were as follows: left ventricular ejection fraction $< 40\%$ by radionuclide angiography, stable clinical symptoms without changes in medication or hospitalizations within 30 days of study inclusion, and optimized standard pharmacological therapy. Subjects with inability to walk on a treadmill, history of unstable angina or myocardial infarction within 3 months of study inclusion, history of snoring, stroke, oxygen use at home, or previously diagnosed with sleep apnea were excluded. Healthy male controls with no history of cardiovascular disease, dyslipidemia, diabetes, or renal insufficiency were recruited by advertisement in subspecialty clinics. Enrolled subjects with heart failure underwent measurement of maximum oxygen consumption ($\text{VO}_2 \text{ max}$) by multistage treadmill exercise test using a modified Bruce

protocol and a 6-min walk under the supervision of a trained nurse [12–15]. All subjects underwent baseline vital signs, height and weight measurements followed by an overnight sleep study and a morning blood draw within 2 weeks of study enrolment. Clinical information collected for all subjects included a complete medical history and medication list, including the use of vitamin supplementation, physical activity, and NYHA classification.

Polysomnography

Nocturnal polysomnography recording consisted of four-channel electroencephalogram, bilateral electrooculogram, submental and anterior tibialis electro-myogram, two lead electrocardiograms, rib cage and abdominal movement by inductive plethysmography, body position, pulse oximetry, and nasal pressure monitoring. Sleep and respiration were scored by a single sleep research technician according to the American Academy of Sleep Medicine guidelines. Exclusion due to obstructive sleep apnea was based on having 10% of all respiratory events obstructive in nature. The oxygen desaturation index was calculated based on the hourly index of oxygen saturation (SaO₂) decrease of 4% during sleep using a beat-to-beat oximetry recording. Cheyne–Stokes respiration was defined as a crescendo–decrescendo pattern of the respiratory airflow signal associated with simultaneous alteration in chest and abdominal wall motion, which were not paradoxical or obstructive in nature. Quantification of Cheyne–Stokes respiration was performed by determining the hourly index of crescendo–decrescendo respiratory cycles (Cheyne–Stokes respiration index) and by adding the duration of all Cheyne–Stokes respiration periods during sleep (Cheyne–Stokes respiration duration) [16].

Quantification of oxidative stress

In the morning following the sleep study, phlebotomy was performed after 30 min of recumbent rest. The formation of reactive oxygen species in neutrophils was measured by flow cytometry. Blood samples were processed within 1 h of collection. Leukocytes from ammonium chloride lysed whole blood were loaded at 4°C with dichlorofluorescein diacetate (Sigma, St. Louis, MO, USA), a non-polar compound that is converted into a non-fluorescent, polar derivative by cellular esterases, then oxidized to fluorescent carboxydichlorofluorescein in the presence of intracellular H₂O₂ and peroxidases following incubation for 30 min at 37°C [17, 18]. Cells were analyzed on a FACSCalibur (BD Biosciences, San Jose, CA, USA). Neutrophils were differentiated from lymphocytes and monocytes by forward- and side-scattered laser light. At least 10,000 neutrophils were analyzed for each subject. The magnitude of reactive oxygen species formation was detected in the fluorescein channel above autofluorescence. Plasma catecholamine levels, brain natriureic peptide (BNP) and C-reactive protein (CRP) were measured in the heart failure group using commercially available radioimmunoassay kits.

Statistical analysis

Data were analyzed using unpaired, two-tailed *t* test for continuous variables and ANOVA with post hoc comparisons by Fisher's exact test for testing multiple factors. All correlation analyses were performed using linear regression.

Results

Twenty-six male patients with heart failure met the inclusion criteria for this study. Three subjects were excluded after undergoing polysomnography due to obstructive sleep apnea. Twenty-three patients with heart failure and 11 healthy controls were available for final analyses. Participants' baseline characteristics and medical history are shown in Table 1. All heart failure subjects were receiving beta-blockers, angiotensin-converting enzyme inhibitors (or angiotensin-receptor blockers), and at least one diuretic. Patients with heart failure were older than controls. The individual values for physiological parameters in the heart failure group are shown in Table 2. Their mean left ventricular ejection fraction was 30.2%.

All patients with heart failure had Cheyne–Stokes respiration during sleep. The baseline characteristics, blood pressure, and sleep parameters for all subjects are shown in Table 3. The mean Cheyne–Stokes respiration index was 43.2 ± 19.3 events/hour (median of 45.4 events/hour) in the heart failure group. Their average sleep time in Cheyne–Stokes respiration was 3.49 ± 1.6 h vs. 0.46 ± 0.38 in the controls (median, 3.58 vs. 0.29). Patients with heart failure had a significantly lower mean SaO_2 during sleep (94.5% vs. 97.8%) and lower SaO_2 nadir (79.2% vs. 88.4%), as compared to healthy controls.

The oxygen desaturation index during sleep was greater in patients with heart failure (25.7 ± 21 events/hour vs. 0.4 ± 0.4 for the controls, $p < 0.001$). It strongly correlated with the hourly index of Cheyne–Stokes respiration cycles ($r = 0.84$, $p < 0.001$) and the duration of Cheyne–Stokes respiration during sleep ($r = 0.74$, $p < 0.005$) in all subjects, as well as within heart failure subjects ($r = 0.77$, $p < 0.001$ and $r = 0.69$, $p < 0.001$, respectively), as displayed in Fig. 1. Oxidative stress was greater in heart failure patients than in controls ($4,218 \pm 1,706$ vs. $1,003 \pm 348$ mean fluorescence intensity/cell, $p < 0.001$).

The mean value of reactive oxygen species formation was not statistically different after dichotomizing the heart failure group according to multiple characteristics, as follows: history of coronary artery disease, hypertension, dyslipidemia, renal insufficiency, or diabetes; the use of individual cardiac medications or statins except for angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker and beta blockers (as all heart failure subjects were taking these medications), the use of vitamins; NYHA class (3); and body mass index (BMI), analyzed by dividing the groups according to BMI categories using two different cutoffs (25 or 30 kg/m²). All subjects had a BMI < 35 kg/m². The vast majority of patients were sedentary, which prevented an accurate analysis of the exercise effect. None of these analyses demonstrated a significant difference in mean values of oxidative stress.

In a second analysis, when dividing heart failure subjects in two groups based on the severity of the Cheyne–Stokes respiration index in relation to the median (45.4 events/hour), there was a significant difference in the arousal index ($p = 0.001$), mean SaO_2 ($p = 0.007$), lowest SaO_2 during sleep ($p < 0.001$), and oxygen desaturation index ($p < 0.001$) between groups. The Cheyne–Stokes duration was longer, and the magnitude of oxidative stress was significantly elevated in the group with a higher Cheyne–Stokes respiration index during sleep ($p < 0.001$ and $p = 0.028$, respectively), as compared to the remaining heart failure subjects. No statistically significant differences in cardiac functional status or sympathetic activation

levels were detected between groups, as shown in Table 4. The higher mean value of VO_2 max seen in heart failure patients with lower indices of Cheyne–Stokes respiration may reflect a better functional state; however, this difference was not statistically significant.

Severity of Cheyne–Stokes respiration, as measured by the Cheyne–Stokes respiration index and duration Cheyne–Stokes respiration during sleep, correlated with mean fluorescence intensity of carboxydichlorofluorescein in neutrophils of patients with heart failure ($r=0.38$, $p=0.06$ and $r=0.44$, $p=0.034$, respectively), as demonstrated in Fig. 2. Multivariate linear regression analyses showed that the total duration of Cheyne–Stokes respiration during sleep was the best independent predictor of oxidative stress in the heart failure group [beta=652 mean fluorescence intensity/cell per hour of Cheyne–Stokes respiration duration (95% CI 312, 992), $p<0.001$]. This relationship was maintained after adjusting for age and BMI, signifying that for each additional hour of Cheyne–Stokes Respiration, the expected increase in reactive oxygen species formation would fall within the confidence interval in 95% of the cases.

The oxygen saturation nadir during sleep correlated inversely with the magnitude of reactive oxygen species formation in patients with heart failure ($p=0.039$) using univariate analysis (Fig. 3). However, this relationship was not maintained after multivariate analyses. No other variable, including measurements of cardiac function, was a significant predictor of oxidative stress in patients with heart failure.

Dopamine levels correlated with the overnight oxygen desaturation index ($r=0.48$, $p=0.03$) and arousal index from sleep ($r=0.51$, $p=0.03$, data not shown). Neither serum catecholamines nor functional measures of heart failure, such as ejection fraction, VO_2 max, total distance in a 6-min walk test, BNP, or CRP levels were significantly correlated with either measures of Cheyne–Stokes respiration or oxidative stress in patients with heart failure.

After a mean follow-up of 4.3 years, 11 of 23 (48%) of the heart failure subjects had died. The mortality rate during this period was greater in the patients with Cheyne–Stokes indices ≥ 45 when compared to heart failure patients with indices <45 events/hour (58.3% vs.33.3%). When comparing the mean values of physiological and sleep-related parameters according to survival in heart failure, the arousal index was higher, and the nadir SaO_2 was lower in the deceased group. There was a trend toward higher oxygen desaturation index and increased oxidative stress in this group ($p=0.09$). This is demonstrated in Table 5. One patient underwent successful heart transplant and was excluded from this analysis.

Discussion

The present data indicate that the duration of Cheyne–Stokes respiration during sleep is an independent predictor of oxidative stress in patients with heart failure. Furthermore, our data confirm that Cheyne–Stokes respiration during sleep is highly prevalent among heart failure patients with decreased left ventricular systolic function who are receiving standard medical therapy [19].

Periodic breathing in heart failure patients is associated with increased mortality regardless of cardiac function [20, 21]. However, the mechanism linking Cheyne–Stokes respiration to mortality in heart failure remains unknown. Oxidative stress is a marker of disease severity and a valuable predictor of mortality in heart failure [22–26]. Our data suggest that increased cellular oxidative stress is a potential link between Cheyne–Stokes respiration and increased mortality.

Traditionally, Cheyne–Stokes respiration has been quantified using an hourly index, having a cutoff for determining presence or absence of disease in heart failure, without establishing levels of disease severity. Given that Cheyne–Stokes is not an all or none phenomena in heart failure, we measured both the hourly index and the total duration of Cheyne–Stokes respiration during the overnight polysomnography, and observed a strong relationship between Cheyne–Stokes respiration and SaO₂ nadir during sleep and increased cellular oxidative stress, independently of echocardiographic indices of heart function and functional status. Our findings suggest that the severity of Cheyne–Stokes respiration is a critical factor associated with the development of oxidative stress, and the duration of Cheyne–Stokes respiration during sleep may be an additional and useful indicator of disease severity in heart failure, being closely correlated with levels of oxidative stress.

The repetitive hypoxia/reoxygenation associated with Cheyne–Stokes breathing in heart failure likely contributes to endothelial and other tissue injury owing to decreased oxygen availability. Under physiological conditions, reactive oxygen species are generated as by-products of oxygen metabolism. When exposed to intermittent hypoxemia, cellular and mitochondrial control of the oxidative pathways is disturbed. Intermittent hypoxia resembles ischemia–reperfusion injury, leading to generation of reactive oxygen species during the reoxygenation period [27]. La Rocca et al. [28] recently demonstrated that the endothelium plays a critical role in the generation of oxidative stress. Endothelial dysfunction may then be further exacerbated by the presence of reactive oxygen species, which could lead to deterioration of cardiac function [29, 30]. Therefore, Cheyne–Stokes respiration during sleep may promote oxidative stress and progressive deterioration of clinical status in patients with heart failure.

Nadir and mean levels of oxygen saturation during sleep, while closely correlated with oxidative stress levels, were not independent predictors of intracellular reactive oxygen species formation in patients with heart failure. This finding highlights the need for using more accurate measures of oxygen availability to the tissue given the intermittent nature of the hypoxia in Cheyne–Stokes respiration [31, 32]. Intermittent hypoxemia has been linked to diurnal increases in blood pressure [33, 34]. The cyclic nature of Cheyne–Stokes respiration may also invoke other mechanisms, such as increased sympathetic activation and sleep fragmentation, which could increase cellular oxidative stress. While elevated sympathetic activation is an established risk factor for mortality in heart failure [35], our study did not find an association between the magnitude of oxidative stress and plasma levels of catecholamines, or measures of sleep fragmentation in patients with heart failure. Nonetheless, a higher arousal index, indicating fragmented sleep, was seen among the deceased patients with heart failure. Plasma dopamine levels were significantly associated with sleep fragmentation and oxygen desaturation index during sleep. It is important to note

that more specific and refined methods for measuring sympathetic activation were not used in this study, bringing forth an important limitation of this negative finding in our sample. Additional limitations of our study include the small sample size, the fact that only men participated in this study, and differences in age between groups, determining our use of adjusted regression models in the analyses concerning heart failure and healthy controls. The prevalence of Cheyne–Stokes respiration in our sample may have been affected by a selection bias. Additionally, the results are only applicable to sleep-related conditions, as Cheyne–Stokes respiration during wakefulness was not assessed by this study.

Several methods have been developed for the measurement of oxidative stress and reactive oxygen species. When comparing results, careful attention should be given to the methodology used as data may not be readily comparable unless strict methodological standardization was applied. The detection of reactive oxygen species using hydrogen peroxide formation in neutrophils used in this study has been shown to correlate with other measurements of oxidative stress [36].

More recently developed techniques to control the respiratory oscillation associated with Cheyne–Stokes respiration, such as adaptive servo ventilation, may have a role in modulating oxidative stress in heart failure, possibly reducing cell damage and impacting mortality by overcoming the respiratory abnormalities during sleep [37, 38]. The potential effects of alternative treatments proposed for Cheyne–Stokes respiration, including cardiac resynchronization, increased carbon dioxide concentration in the inhaled air, use of supplemental oxygen, and positional changes, also deserve further investigation [39–48]. It remains to be seen if the use of antioxidants could counteract some of the effects seen in this study.

During clinical assessment of heart failure patients with Cheyne–Stokes respiration, special consideration should be given to using the currently available techniques for overcoming this respiratory abnormality while awaiting more clinical and research data on outcome.

In conclusion, the present data implicate the generation of cellular oxidative stress as a potential link to cell injury in heart failure patients with Cheyne–Stokes respiration. This pathway could lead to progression of myocardial failure and increased mortality. Further studies are needed to ascertain whether treatment of Cheyne–Stokes respiration would lead to decreased oxidative stress and improved patient outcome [25, 49].

Acknowledgments

We would like to thank Ming Chen and Vanessa Coradin at the NYU Sleep Disorder Center for assistance in the performance and scoring of the sleep studies, Daniel Meyer and Michael Gregory at the Flow Cytometry Core for their contribution in performing the flow cytometry analyses, and Dr. Robert Kaner for his valuable comments in reviewing the manuscript.

Grant support: American Heart Association National Center, Scientist Development Award and National Institutes of Health.

References

1. Mortara A, Sleight P, Pinna GD, Maestri R, Capomolla S, Febo O, La Rovere MT, Cobelli F. Association between hemodynamic impairment and Cheyne–Stokes respiration and periodic breathing in chronic stable congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1999; 84(8):900–904. doi:S0002-9149(99)00462-2. [PubMed: 10532507]
2. Fanfulla F, Mortara A, Maestri R, Pinna G, Bruschi C, Cobelli F, Rampulla C. The development of hyperventilation in patients with chronic heart failure and Cheyne–Stokes respiration. *Chest.* 1998; 114(4):1083–1090. DOI: 10.1378/chest.114.4.1083 [PubMed: 9792581]
3. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation.* 1998; 97(21):2154–2159. [PubMed: 9626176]
4. Lofaso F, Verschueren P, Rande J, Harf A, Goldenberg F. Prevalence of sleep-disordered breathing in patients on a heart transplant waiting list. *Chest.* 1994; 106(6):1689–1694. DOI: 10.1378/chest.106.6.1689 [PubMed: 7988185]
5. Bradley TD, Floras JS. Sleep apnea and heart failure. Part II: central sleep apnea. *Circulation.* 2003; 107(13):1822–1826. DOI: 10.1161/01.cir.0000061758.05044.64 [PubMed: 12682029]
6. Hanly P, Zuberi-Khokhar N. Increased mortality associated with Cheyne–Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med.* 1996; 153(1):272–276. [PubMed: 8542128]
7. Francis DP, Willson K, Davies LC, Coats AJS, Piepoli M. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. *Circulation.* 2000; 102(18):2214–2221. [PubMed: 11056095]
8. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, Giannuzzi P. Prognostic value of nocturnal Cheyne–Stokes respiration in chronic heart failure. *Circulation.* 1999; 99(11):1435–1440. [PubMed: 10086966]
9. Fanfulla F, Mortara A, Maestri R, Pinna GD, Bruschi C, Cobelli F, Rampulla CU. The development of hyperventilation in patients with chronic heart failure and Cheyne–Stokes respiration: a possible role of chronic hypoxia. *Chest.* 1998; 114(4):1083–1090. [PubMed: 9792581]
10. Corra U, Pistono M, Mezzani A, Braghiroli A, Giordano A, Lanfranchi P, Bosimini E, Gnemmi M, Giannuzzi P. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation.* 2006; 113(1):44–50. DOI: 10.1161/circulationaha.105.543173 [PubMed: 16380551]
11. Bradley TD. The ups and downs of periodic breathing: Implications for mortality in heart failure. *J Am Coll Cardiol.* 2003; 41(12):2182–2184. DOI: 10.1016/s0735-1097(03)00470-4 [PubMed: 12821244]
12. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC. Acc/aha guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *J Heart Lung Transplant.* 2002; 21(2):189–203. doi:S1053249801007768. [PubMed: 11834347]
13. Remme WJ, Swedberg K. Comprehensive guidelines for the diagnosis and treatment of chronic heart failure. Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. *Eur J Heart Fail.* 2002; 4(1):11–22. doi:S1388984201002318. [PubMed: 11812661]
14. Guyatt G, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J.* 1985; 8(132):919–923.
15. Lipkin DP, Scriven A, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *Br Med J (Clin Res Ed).* 1986; 292(6521):653–655.

16. Krieger AC, Ayappa I, Norman RG, Rapoport DM. Central vs. Obstructive respiratory events classified by nasal cannula/pressure transducer. *Am J Respir Crit Care Med*. 2000; 161:A28. Abstract.
17. Himmelfarb J, Hakim RM, Holbrook DG, Leeber DA, Ault KA. Detection of granulocyte reactive oxygen species formation in whole blood using flow cytometry. *Cytometry*. 1992; 13(1):83–89. [PubMed: 1372205]
18. Bass D, Parce J, Dechatelet L, Szejda P, Seeds M, Thomas M. Flow cytometric studies of oxidative product formation by neutrophils: a graded response to membrane stimulation. *J Immunol*. 1983; 130(4):1910–1917. [PubMed: 6833755]
19. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009; 53(15):e1–e90. DOI: 10.1016/j.jacc.2008.11.013 [PubMed: 19358937]
20. Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne–Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med*. 1996; 153(1):272–276. [PubMed: 8542128]
21. Javaheri S, Shukla R, Zeigler H, Wexler L. 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. DOI: 10.1016/j.jacc.2007.01.084 [PubMed: 17512359]
22. Eleuteri EMF, Gnemmi I, Carbone M, Colombo M, La Rocca G, Anzalone R, Tarro Genta F, Zummo G, Di Stefano A, Giannuzzi P. Role of oxidative and nitrosative stress biomarkers in chronic heart failure. *Front Biosci*. 2009; 14:2230–2237.
23. Michowitz Y, Kisil S, Guzner-Gur H, Rubinstein A, Wexler D, Sheps D, Keren G, George J. Usefulness of serum myeloperoxidase in prediction of mortality in patients with severe heart failure. *IMAJ*. 2008; 12:884–888.
24. Keith M, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, Jeejeebhoy KN. Increased oxidative stress in patients with congestive heart failure. *J Am Coll Cardiol*. 1998; 31(6): 1352–1356. doi:S0735-1097(98)00101-6. [PubMed: 9581732]
25. Mak S, Newton GE. The oxidative stress hypothesis of congestive heart failure: radical thoughts. *Chest*. 2001; 120(6):2035–2046. [PubMed: 11742938]
26. Poletti R, Passino C, Giannoni A, Zyw L, Prontera C, Bramanti F, Clerico A, Piepoli M, Emdin M. Risk factors and prognostic value of daytime Cheyne–Stokes respiration in chronic heart failure patients. *Int J Cardiol*. 2009; 137(1):47–53. [PubMed: 18691782]
27. Tan S, Zhou F, Nielsen VG, Wang Z, Gladson CL, Parks DA. Increased injury following intermittent fetal hypoxia–reoxygenation is associated with increased free radical production in fetal rabbit brain. *J Neuropathol Exp Neurol*. 1999; 58(9):972–981. [PubMed: 10499439]
28. La Rocca G, Di Stefano A, Eleuteri E, Anzalone R, Magno F, Corrao S, Loria T, Martorana A, Di Gangi C, Colombo M, Sansone F, Patanè F, Farina F, Rinaldi M, Cappello F, Giannuzzi P, Zummo G. Oxidative stress induces myeloperoxidase expression in endocardial endothelial cells from patients with chronic heart failure. *Basic Res Cardiol*. 2009; 104(3):307–320. [PubMed: 19030913]
29. Takenaka H, Kihara Y, Iwanaga Y, Onozawa Y, Toyokuni S, Kita T. Angiotensin ii, oxidative stress, and extracellular matrix degradation during transition to lv failure in rats with hypertension. *J Mol Cell Cardiol*. 2006; 41(6):989–997. [PubMed: 16979182]
30. Zhang P, Hou M, Li Y, Xu X, Barsoum M, Chen Y, Bache RJ. NADPH oxidase contributes to coronary endothelial dysfunction in the failing heart. *Am J Physiol Heart Circ Physiol*. 2009; 296(3):H840–H846. DOI: 10.1152/ajpheart.00519.2008 [PubMed: 19168727]
31. Prabhakar NR. Oxygen sensing during intermittent hypoxia: cellular and molecular mechanisms. *J Appl Physiol*. 2001; 90(5):1986–1994. [PubMed: 11299293]
32. Gottlieb JD, Schwartz AR, Marshall J, Ouyang P, Kern L, Shetty V, Trois M, Punjabi NM, Brown C, Najjar SS, Gottlieb SS. Hypoxia, not the frequency of sleep apnea, induces acute hemodynamic

- stress in patients with chronic heart failure. *J Am Coll Cardiol*. 2009; 54(18):1706–1712. DOI: 10.1016/j.jacc.2009.08.016 [PubMed: 19850211]
33. Fletcher EC, Lesske J, Qian W, Miller CC, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension*. 1992; 19(6 Pt 1):555–561. [PubMed: 1592450]
 34. Bao G, Metreveli N, Li R, Taylor A, Fletcher EC. Blood pressure response to chronic episodic hypoxia: role of the sympathetic nervous system. *J Appl Physiol*. 1997; 83(1):95–101. [PubMed: 9216950]
 35. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol*. 2009; 54(5):375–385. DOI: 10.1016/j.jacc.2009.03.061 [PubMed: 19628111]
 36. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med*. 2002; 165(7):934–939. [PubMed: 11934717]
 37. Bitter T, Westerheide N, Faber L, Hering D, Prinz C, Langer C, Horstkotte D, Oldenburg O. Adaptive servoventilation in diastolic heart failure and Cheyne–Stokes respiration. *Eur Respir J*. 2010; 36:385–392. DOI: 10.1183/09031936.00045609 [PubMed: 20032021]
 38. Oldenburg O, Bitter T, Schmidt A, Wellmann B, Lehmann R, Prinz C, Langer C, Horstkotte D. Treatment of nocturnal cheyne - stokes - respiration by adaptive servoventilation improves sleep disordered breathing and cardiopulmonary function in patients with chronic heart failure. *Circulation*. 2008; 118(18):S717A. abstract.
 39. Olson LJ, Somers VK. Treating central sleep apnea in heart failure: outcomes revisited. *Circulation*. 2007; 115(25):3140–3142. DOI: 10.1161/circulationaha.107.709303 [PubMed: 17592088]
 40. Scharf C, Turk A, Brack T, Bloch K. Cardiac resynchronization therapy, central sleep apnea, and Cheyne–Stokes respiration in chronic heart failure patients. *J Am Coll Cardiol*. 2005; 45(4):633. doi: 10.1016/j.jacc.2004.11.028 [PubMed: 15708718]
 41. Sinha AM, Skobel EC, Breithardt OA, Norra C, Markus KU, Breuer C, Hanrath P, Stellbrink C. Cardiac resynchronization therapy improves central sleep apnea and Cheyne–Stokes respiration in patients with chronic heart failure. *J Am Coll Cardiol*. 2004; 44(1):68–71. DOI: 10.1016/j.jacc.2004.03.040 [PubMed: 15234409]
 42. Stellbrink C, Skobel E, Sinha AM. Cardiac resynchronization therapy, central sleep apnea, and Cheyne–Stokes respiration in chronic heart failure patients: reply. *J Am Coll Cardiol*. 2005; 45(4):633–634. DOI: 10.1016/j.jacc.2004.11.027 [PubMed: 15708718]
 43. Andreas S, Weidel K, Hagenah G, Heindl S. Treatment of Cheyne–Stokes respiration with nasal oxygen and carbon dioxide. *Eur Respir J*. 1998; 12(2):414–419. [PubMed: 9727794]
 44. Franklin KA, Eriksson P, Sahlin C, Lundgren R. Reversal of central sleep apnea with oxygen. *Chest*. 1997; 111(1):163–169. [PubMed: 8996011]
 45. Krachman SL, D'Alonzo GE, Berger TJ, Eisen HJ. Comparison of oxygen therapy with nasal continuous positive airway pressure on Cheyne–Stokes respiration during sleep in congestive heart failure. *Chest*. 1999; 116(6):1550–1557. [PubMed: 10593775]
 46. Soll BA, Yeo KK, Davis JW, Seto TB, Schatz IJ, Shen EN. The effect of posture on Cheyne–Stokes respirations and hemodynamics in patients with heart failure. *Sleep*. 2009; 32(11):499–506. [PubMed: 19413144]
 47. Lorenzi-Filho G, Rankin F, Bies I, Bradley TD. Effects of inhaled carbon dioxide and oxygen on Cheyne–Stokes respiration in patients with heart failure. *Am J Respir Crit Care Med*. 1999; 159(5):1490–1498. [PubMed: 10228116]
 48. Andreas S, Clemens C, Sandholzer H, Figulla H, Kreuzer H. Improvement of exercise capacity with treatment of Cheyne–Stokes respiration in patients with congestive heart failure. *J Am Coll Cardiol*. 1996; 27(6):1486–1490. [PubMed: 8626963]
 49. 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):473–47. [PubMed: 7633695]

Fig. 1. Relationship between measures of Cheyne–Stokes respiration during sleep and oxygen desaturation during sleep in heart failure ($n=23$)

Fig. 2. Relationship between measures of Cheyne–Stokes respiration during sleep and the intensity of reactive oxygen species formation in neutrophils in subjects with heart failure ($n=23$)

Fig. 3. Relationship between oxygen saturation nadir during sleep and oxidative stress in heart failure subjects ($n=23$)

Table 1
Baseline demographic and clinical characteristics of all subjects

	Heart failure patients (<i>n</i> =23)	Healthy controls (<i>n</i> =11)
	Mean±SD	Mean±SD
Age (years) *	66.2±10.1	38.7±8.8
Body mass index (kg/m ²)	27.7±3.5	25.6±3.3
<i>n</i> (%)	<i>n</i> (%)	
Ethnicity		
White	4 (17.4%)	4 (36.4%)
Black	9 (39.1%)	3 (27.3%)
Hispanic	10 (43.5%)	4 (36.4%)
Medical history		
Coronary artery disease	11 (47.8%)	0
Prior myocardial infarction	7 (30.4%)	0
Hypertension	10 (43.5%)	0
Dyslipidemia	7 (30.4%)	0
Renal insufficiency	7 (30.4%)	0
Diabetes	9 (39.1%)	0
Medications		
Aspirin	18 (78.3%)	0
ACEI/ARB	23 (100%)	0
Beta blocker	23 (100%)	0
Digoxin	13 (56.5%)	0
Furosemide	19 (82.6%)	0
Hydralazine	4 (17.4%)	0
Spironolactone	15 (65.2%)	0
Statins	16 (69.6%)	0

SD standard deviation, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker

*
 $p < 0.05$

Table 2
Measures of cardiac function and sympathetic activity in the heart failure group

Subject	EF (%)	VO ₂ (kg/m)	6mw (ft)	CRP (mg/L)	BNP (pg/mL)	NE (pg/mL)	EPI (pg/mL)	DA (pg/mL)
1	39	33.0	1,300	8.2	422	480	32	11
2	40	9.3	1,200	4.1	520	376	20	13
3	25	25.7	1,200	3.7	66	291	36	12
4	13	13.1	450	13.1	3,250	832	79	27
5	40	12.9	800	4.5	67	323	14	11
6	37	25.9	1,125	0.4	621	302	64	16
7	40	3.5	675	18.3	253	486	22	5
8	27	2.3	375	6.7	566	528	5	6
9	26	12.3	775	3.5	272	244	15	11
10	37	9.6	1,200	3.5	151	562	44	15
11	33	11.0	690	2.7	67	234	5	5
12	23	14.7	1,100	3.9	266	278	13	5
13	37	16.3	1,125	8.0	355	660	21	43
14	24	1.5	500	2.6	135	488	19	11
15	38	18.6	1,125	1.2	116	460	36	23
16	31	12.8	900	0.3	419	390	11	5
17	13	17.9	1,200	8.1	2,270	620	14	13
18	20	1.6	1,010	24.4	168	396	10	10
19	15	5.3	890	11.2	198	157	5	21
20	35	7.0	450	0.9	213	693	62	21
21	38	14.0	800	22.9	3,272	354	24	13
22	35	16.9	1,000	2.7	68	183	17	5
23	28	7.0	725	1.5	226	539	5	13
Mean	30.17	12.70	896.30	6.80	607.00	429.39	24.91	13.70
SD	9.06	8.09	280.86	6.90	949.84	173.05	20.36	8.84

Normal range for supine values: norepinephrine=70–750 pg/mL, epinephrine=0–110 pg/mL and dopamine=0–30 pg/mL

EF=ejection fraction, VO₂=maximum oxygen consumption, 6mw=6-min walk distance, CRP=C-reactive protein, BNP=brain natriuretic peptide, NE=plasma norepinephrine, EPI=plasma epinephrine, DA=plasma dopamine, SD=standard deviation

Table 3
Physiological and sleep related parameters in all subjects

	Heart failure subjects Mean±SD (n=23)	Controls Mean±SD (n =11)	p value (two-tailed)
Heart rate (bpm) *	75.1±14.4	60.0±9.2	0.005
Systolic BP (mmHg) *	129.7±26.9	108.0±10.1	0.020
Diastolic BP (mmHg) *	69.3±11.7	59.8±4.3	0.019
Total sleep time (min)	314±88	361 ±46	0.106
Arousal index (events/hour) *	30.9±13.9	9.3±3.4	<0.001
CSR index (events/hour) *	43.2±19.3	0.56±0.67	<0.001
CSR duration (h) *	3.49±1.6	0.46±0.38	<0.001
Mean SaO ₂ sleep (%) *	94.5±2.8	97.8±1.4	0.001
Lowest SaO ₂ sleep (%) *	79.2±9.9	88.4±6.3	0.008
ODI (events/h) *	25.7±21.0	0.4±0.4	<0.001
ROS (MFI/cell) *	4,218±1,706	1,003±348	<0.001

SD standard deviation, *BP* blood pressure, *CSR* Cheyne–Stokes respiration, *SaO₂* oxygen saturation, *ODI* oxygen desaturation index, *ROS* reactive oxygen species, *MFI* mean fluorescence index

*
p<0.05

Table 4
Physiological and respiratory related parameters in the heart failure subjects

	CSR index <45 events/hour Mean±SD (n=11)	CSR index ≥45 events/hour Mean±SD (n=12)	p value (two-tailed)
Age (years)	66.5±11.3	65.9±9.2	0.901
Body mass index (kg/m ²)	27.1 ±3.3	29.3±3.1	0.206
Heart rate (bpm)	74.1 ±14.6	76.0±14.8	0.759
Systolic BP (mmHg)	128.6±28.9	130.8±26.3	0.856
Diastolic BP (mmHg)	68.7±11.4	69.8±12.4	0.839
Ejection fraction (%)	31.0±8.9	29.4±9.6	0.686
VO ₂ max (kg/m)	15.4±10.6	10.7±6.2	0.216
6-min walk distance (ft)	881 ±320	910±253	0.808
CRP (mg/L)	6.0±5.5	7.6±8.7	0.626
BNP (pg/mL)	558±966	676±1,064	0.793
NE plasma (pg/mL)	408±192	449±177	0.616
Epi plasma (pg/mL)	29.7±25.5	20.4±16.5	0.327
DA plasma (pg/mL)	10.6±7.7	16.1 ± 10.7	0.237
Total sleep time (min)	299±104	332±73	0.322
Arousal index (events/hour) *	22.1±7.2	39±12.9	0.001
CSR duration (hours) *	2.14±0.6	4.74±1.02	<0.001
Mean SaO ₂ sleep (%) *	96.1 ±1.6	93.1 ±2.9	0.007
Lowest SaO ₂ sleep (%) *	86.5±5.3	72.5±8.2	<0.001
ODI (events/hour) *	9.2±10.4	42.3±14.6	<0.001
ROS (MFI/cell) *	3,421 ±1,944	4,949±1,083	0.028

CSR Cheyne–Stokes respiration, SD standard deviation, BP blood pressure, VO₂ max maximum oxygen consumption, CRP C-reactive protein, BNP brain natriuretic peptide, NE norepinephrine, Epi epinephrine, DA dopamine, SaO₂ oxygen saturation, ODI oxygen desaturation index, ROS reactive oxygen species, MFI mean fluorescence intensity

*
p<0.05

Table 5
Physiological and respiratory-related parameters in the heart failure subjects according to survival

	Alive N=11	Deceased N=11	<i>p</i> value
Age (years)	65.5±10.8	66.9±10.3	0.749
Body mass index (kg/m ²)	26.5±3.7	28.7±3.1	0.149
Heart rate (bpm)	78.2±10.5	74.7±15.7	0.551
Systolic BP (mmHg)	129.7±27.9	132.3±27.0	0.830
Diastolic BP (mmHg)	67.3±10.8	72.1±12.7	0.349
Ejection fraction (%)	32.7±7.5	26.7±9.7	0.121
VO ₂ max (kg/m)	13.4±10.5	12.0±5.7	0.698
6-min walk distance (ft)	952.3±272.6	849.1±304.0	0.412
CRP (mg/L)	8.6±8.8	5.2±4.4	0.277
BNP (pg/mL)	540.6±924.2	722.5±1,040.2	0.669
NE serum (pg/mL)	383.0±109.9	485.5±216.5	0.177
Epi serum (pg/mL)	26.5±16.8	24.4±24.8	0.819
DA serum (pg/mL)	11.1 ±3.5	16.5± 11.9	0.162
Total sleep time (min)	322.8±92.3	308.5±91.5	0.718
Arousal index (events/hour)*	25.2±8.6	36.9±16.0	0.046
CSR duration (hours)	3.1±1.3	4.1 ± 1.7	0.141
CSR index (cycles/h)	39.0±21.9	48.6±16.3	0.253
Mean SaO ₂ sleep (%)	94.9±2.4	94.1±3.3	0.578
SaO ₂ nadir (%) ^a	83.0±7.5	74.6±10.6	0.045
ODI (events/hour)	18.7±18.9	34.2±20.7	0.090
Oxidative stress (MFI/cell)	3,601.0±1,871.4	4,853.0±1,427.1	0.093

BP blood pressure, *VO₂ max* maximum oxygen consumption, *CRP* C-reactive protein, *BNP* brain natriuretic peptide, *NE* norepinephrine, *Epi* epinephrine, *DA* dopamine, *SaO₂* oxygen saturation, *ODI* oxygen desaturation index, *ROS* reactive oxygen species, *MFI* mean fluorescence intensity

*
p<0.05