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PRO/CON DEBATE

Routine Polysomnography is Not Indicated in Congestive Heart Failure

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This article takes the con position, i.e., that routine sleep studies are not indicated in patients with heart failure (HF). Simply put, the evidence is currently insufficient to recommend this expensive diagnostic strategy. This statement is based on analysis of what we know about the following: the epidemiology of this problem in this patient group; case identification strategies; most importantly, benefits of treatment of sleep-disordered breathing in patients with HF; as well as an analysis of likely costs of the strategy. Before we address these issues, we first address some definitional questions.

Sleep-disordered breathing in heart failure is said to exist in two varieties,[1,2] i.e., central sleep apnea occurring during Cheyne-stokes respiration (for definitions, see reference 3) and obstructive sleep apnea (for definitions, reference 3). These are both said to occur commonly in patients with congestive heart failure.[1,2, 4-8] Cheyne-Stokes respiration is the result of an oscillatory cyclical neural output to the diaphragm.[2] This occurs when overall loop gain is sufficiently high and there is unstable operation of the ventilatory control system leading to self-sustaining oscillations.[9-11] Both chemoreceptor gain[12,13] and the apnea threshold for CO_2 that is found during sleep[14] play a role. But oscillatory output will also affect output to upper airway dilator muscles, hence facilitating development of obstructive sleep apnea in susceptible individuals. Thus, at a pathogenetic level these are not totally separable disorders. Clinically, both commonly exist in the same individual and the frequency of each type of event may vary across a single night.[15] Thus, there are mixed distributions of types of respiratory events during sleep in individual subjects. (These mixed distributions should not be confused with mixed individual apneas or hypopneas.) Unfortunately, there is no consistency in the criteria used as to what constitutes primarily obstructive events, as compared to central. Some recent studies, for example, use a definition for obstructive sleep apnea of having >50% of events being obstructive in nature,[16] while another study uses ≥80% of events being obstructive to qualify as obstructive sleep apnea.[17] This issue is further compounded by problems in identifying whether an individual event is central or obstructive from surface measurements, i.e., without esophageal pressure monitoring.[18] Nevertheless, despite these major issues, the literature in this area treats central and obstructive sleep-disordered breathing as if they were separate processes.[1,2] This artificial distinction may have impeded progress in this area.

Much of the investigation in this area, at least until recently, has focused on central sleep apnea. An early study suggested that this was extremely common in patients with heart failure. Defined as an apnea-hypopnea index >15 episodes/hour, this occurred in 40% of patients.[4] This early study (see also Table 1) was based on a case series from one institution (a Veterans Administration Medical Center). Other case series have followed (see references 5-8 and Table 1), all with a relatively limited sample size apart from the study of Sin et al with 450 subjects.[7] But this latter study cannot be used to define prevalence, since individuals investigated in this study were referred to a sleep center for evaluation because of suspicions they had problems with their sleep. Thus, this is a very biased sample! If this study is not considered, the other studies are too small to give accurate estimates of prevalence. Not surprisingly, these studies do not give confidence intervals for their estimates of prevalence, which will be large as a result of the small sample sizes. The samples are not robust from an epidemiological viewpoint since they are mostly case series from individual institutions. Moreover, and most importantly, these studies were largely done before the recent changes in management of systolic dysfunction in HF. (All of the current literature on sleep-disordered breathing is for systolic dysfunction, not for diastolic dysfunction.) These recent changes have resulted in more aggressive medical management, focusing on neurohormonal blockade of the renin-angiotensin-aldersterone and adrenergic systems as well as applying novel pacing strategies. (for new guidelines, see reference 19). The report of an average systolic blood pressure of 120 mm Hg in the report of Javaheri et al,[4] as compared to the much more aggressive current therapeutic target of 90 to 110 mm Hg[20] indicates that these patients were inadequately treated based on today's standards. Moreover, in the study of Solin et al,[5] the group with central sleep apnea had a mean wedge pressure of 22.8±1.2 mm Hg. This is significantly higher than would be considered acceptable after aggressive "tailored" medical management[21] and higher than in the group with no apneas (11.5±1.3 mm Hg). Thus, the apparent high prevalence in these small case series may simply be a consequence of inadequate medical man-

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agement in some patients. Further support for this hypothesis also comes from the study of Solin et al[5] who showed both a correlation between central apnea-hypopnea index and pulmonary capillary wedge pressure (r=0.47, p=0.006) as well as reductions in frequency of respiratory events as wedge pressure was reduced by intensive medical therapy (see Figure 2, reference 5). These studies were also largely done before the recent widespread use of beta-blockers in this patient population, as a result of large randomized clinical trials.[22-26] Since beta-blockers can reduce the increase in the ventilatory response to hypoxia that is produced by norepinephrine,[27] it is arguable that this will directly reduce the likelihood of Cheyne-Stokes respiration. (Reductions in the ventilatory response will lead to increased stability of the ventilatory control system, i.e., less tendency to oscillate.) In addition, beta blockers have been shown to promote remodeling of the failing ventricle and over time may improve cardiac performance. As the heart improves, the cardiac index may improve ameliorating some of the pathogenetic mechanisms for central sleep apnea. Several other more recent interventions have also been shown to improve heart function, heart failure symptoms and survival. Biventricular pacing is rapidly becoming the standard of care in appropriate patients with advanced heart failure.[28] This therapy can also improve cardiac index and lead to "positive" remodeling. There is, moreover, a provocative study that showed that atrial pacing improves obstructive sleep apnea.[29] Thus, we currently know very little about the current epidemiology of sleep-disordered breathing in patients with HF, with either systolic or diastolic dysfunction, and we cannot answer the very basic question, i.e., how common is sleep-disordered breathing in patients with HF when modern medical management is used? And which of the current medical or device strategies now used for treatment of heart failure improve sleep-disordered breathing?

One argument that Dr. Naughton will likely advance to argue that sleep studies need to be done is that it is difficult clinically to determine who is likely to have central sleep apnea. (The clinical features of obstructive sleep apnea are well known and are not repeated here.[30]) The problem, of course, is that nobody has done the necessary investigation. We do know that there are definite risk factors for the presence of Cheyne-Stokes respiration, i.e., older age, male gender, presence of atrial fibrillation and a lower $PaCO_2$.[7] But how useful this clinical information is in identifying patients with HF, who are likely to have Cheyne-Stokes respiration, has never been addressed prospectively. It seems important that such studies are done before simply recommending a study on everybody!

The key issue, before proposing to do sleep studies on everybody with HF, and hence identify individuals with HF who have sleep-disordered breathing, is to consider whether treatment benefits these individuals. Unfortunately, this is where the data are weakest and there are no definitive data that there are treatment benefits in this patient group. Initial studies focused on treatment of Cheyne-Stokes respiration by nasal continuous positive airway pressure (CPAP)[31-36] although both oxygen[37-41] and other positive pressure modalities have been used.[42, 43] Early, somewhat small, studies by Dr. Naughton and colleagues showed increases in left ventricular ejection fraction with CPAP[31] and reductions in catecholamine levels[32] as compared to normal medical management, i.e., without specifically addressing sleep-disordered breathing. But changes in these intermediate end-points do not of necessity extrapolate into changes in more meaningful hard cardiological end-points, e.g., transplant free survival time. There are several examples of drugs that improve exercise capacity, heart failure symptoms and ejection fraction that are associated with worsening survival in heart failure. Despite very promising early small studies, inotropic drugs (adrenergic agonists as well as phosphodiesterase inhibitors with both intravenous and oral formulations) show impressive acute improvements but have all been associated with increased risk of death.[44] For this reason, large scale multicentered clinical trials that are designed to evaluate transplant free survival are necessary before benefit can be assessed. The effect of CPAP on transplant free survival has been addressed in the study of Sin et al.[36] In this study, 14 patients were randomized to CPAP and 15 to normal medical management. Over a follow-up period of the order of 42 months, there was no significant difference in transplant free survival in an intent to treat analysis between the groups (p=0.101). But when the two patients on the CPAP treatment arm who did not use CPAP were excluded, the differences were significant (p=0.047). Hardly, a ringing endorsement of the efficacy of this approach. There are, moreover, contrary data. A very small study conducted in Oxford (n=-6) found no improvement in left ventricular ejection fraction with CPAP in patients with HF.[33] Despite the problems with these small studies on efficacy and safety, investigators have moved, perhaps too rapidly, to a large multi-center trial in Canada on effect of CPAP on transplant free survival time. This study is called the CANPAP study (for details, see reference 45). The study has been ongoing for many years and results of this study are eagerly awaited. It is a critical piece of data to have before making any recommendations about diagnostic strategies.

While the jury is still out with respect to benefit of treating Cheyne-Stokes respiration in such patients, investigators in this area are already "jumping ship" and two recent studies,[16, 17] one from Dr. Naughton's group,[17] have begun to study the benefit of treating obstructive sleep apnea. The same paradigm that was used for Cheyne-Stokes respiration is being followed and both of

Table 1—Proportion of patients with HF who had Cheyne-Stokes or obstructive apnea in different studies

Reference	N	% with Cheyne-Stokes	% OSA	Comment
Javaheri et al, Circ 97:2154, 1998 [4]	81	40	11	Case series: pre-beta blockers
Sin et al, AJRCCM 160:1101, 1999 [7]	450	29	32	Pre-beta blocker; referred to sleep program; not generalizable sample (AHI>15)
Solin et al, Circ 99:1574, 1999 [5]	75	44	27	Case series: pre-beta blockers
Tremel et al, Eur Heart J 20:1201, 1999 [6]	34	62	21	Small case series; pre-beta blockers
Lanfranchi et al, Circ 107:727, 2003 [8]	47	55	11	Small case series; about 40% on beta blockers

these small studies—24 (12 on CPAP, 12 control)[16] and 55 (28 on CPAP, 27 control)—have shown improvement in left ventricular ejection fraction after one month[16] and 3 months, respectively.[17] It is to be hoped that investigators in this area build a more robust base on likely treatment efficacy, as well as safety, before embarking on another large phase 3 randomized control clinical trial.

While we know little about benefit, we can provide some estimate of cost of the strategy proposed by Dr. Naughton. If we use figures from the American Heart Association, there are 5 million patients in the United States alone with a diagnosis of congestive heart failure. If we use a round figure of $1,000/sleep study, the expense of Dr. Naughon's proposal is $5 billion in the first year. Moreover, there are continued costs since 550,000 new patients with HF are identified each year. Thus, the annual recurring costs would be $550 million/annum. While one might quibble about the exact numbers, no matter what assumptions one makes, these are big expenses. We would do our part to contribute to the growing fiscal deficit in the United States. These large expenses are being justified based on small trials using intermediate endpoints and one small study in which transplant free survival was assessed, and was only significant when two subjects in the CPAP treatment group were excluded from the analyses. If you buy this, we have a bridge in Philadelphia that we are selling!

In conclusion, the evidence is totally lacking for Dr. Naughton to advocate doing sleep studies in all patients with heart failure. Investigators in this area need to avoid such hype and return to basics. We need robust epidemiological studies; studies on case identification; more in-depth studies on safety and efficacy before proceeding to randomized clinical trials. It is tempting to jump to the final answer but scientific investigation is built, albeit at times tediously, brick by brick.

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REFERENCES

1. Bradley TD, Floras JS. Sleep apnea and heart failure: Part I: obstructive sleep apnea. Circulation 2003;107:1671-1678.
2. Bradley TD, Floras JS. Sleep apnea and heart failure: Part II: central sleep apnea. Circulation 2003;107:1822-1826.
3. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-689.
4. 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;97:2154-2159.
5. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 1999;99:1574-1579.
6. Tremel F, Pepin JL, Veale D, Wuyam B, Siche JP, Mallion JM, Levy P. High prevalence and persistence of sleep apnoea in patients referred for acute left ventricular failure and medically treated over 2 months. Eur Heart J 1999;20:1201-1209.
7. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160:1101-1106.
8. 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;107:727-732.
9. Cherniack NS. Apnea and periodic breathing during sleep. N Engl J Med 1999;341:985-987.
10. Hall MJ, Xie A, Rutherford R, Ando S, Floras JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. Am J Respir Crit Care Med 1996;154:376-381.
11. Pinna GD, Maestri R, Mortara A, La Rovere MT, Fanfulla F, Sleight P. Periodic breathing in heart failure patients: testing the hypothesis of instability of the chemoreflex loop. J Appl Physiol 2000;89:2147-2157.
12. Topor ZL, Johannson L, Kasprzyk J, Remmers JE. Dynamic ventilatory response to CO_2 in congestive heart failure patients with and without central sleep apnea. J Appl Physiol 2001;91:408-416.
13. Solin P, Roebuck T, Johns DP, Walters EH, Naughton MT. Peripheral and central ventilatory responses in central sleep apnea with and without congestive heart failure. Am J Respir Crit Care Med 2000;162:2194-2200.
14. Xie A, Skatrud JB, Puleo DS, Rahko PS, Dempsey JA. Apnea-hypopnea threshold for CO2 in patients with congestive heart failure. Am J Respir Crit Care Med 2002;165:1245-1250.
15. Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO2 and circulatory delay. Circulation 2001;103:238-243.
16. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348:1233-1241.
17. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med 2004;169:361-366.
18. Boudewyns A, Willemen M, Wagemans M, De Cock W, Van de Heyning P, De Backer W. Assessment of respiratory effort by means of strain gauges and esophageal pressure swings: a comparative study. Sleep 1997;20:168-170.
19. 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, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC, Jr. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.
20. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-1252.
21. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. Eur J Heart Fail 1999;1:251-257.
22. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. Lancet 1997;349:375-380.
23. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-2007.
24. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB,

Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 1996;94:2807-2816.
25. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, Krueger SK, Hershberger R, Uretsky BF, Bowers JA, Sackner-Bernstein JD, Young ST, Holcslaw TL, Lukas MA. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. Circulation 1996;94:2800-2806.
26. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-1658.
27. Heistad DD, Wheeler RC, Mark AL, Schmid PG, Abboud FM. Effects of adrenergic stimulation on ventilation in man. J Clin Invest 1972;51:1469-1475.
28. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-1853.
29. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, Tunon De Lara M, Haissaguerre M, Clementy J. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002;346:404-412.
30. Schwab RJ, Goldberg AN, Pack AI. Sleep apnea syndromes. In A. P. Fishman, J. A. Elias, J. A. Fishman, M. A. Grippi, L. R. Kaiser and R. M. Senior, Editors. Pulmonary Diseases and Disorders, third edition. New York: McGraw-Hill; 1998;1617-1637.
31. Naughton MT, Liu PP, Bernard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. Am J Respir Crit Care Med 1995;151:92-97.
32. 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;152:473-479.
33. Davies RJ, Harrington KJ, Ormerod OJ, Stradling JR. Nasal continuous positive airway pressure in chronic heart failure with sleep-disordered breathing. Am Rev Respir Dis 1993;147:630-634.
34. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 2000;101:392-397.
35. Tkacova R, Liu PP, Naughton MT, Bradley TD. Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. J Am Coll Cardiol 1997;30:739-745.
36. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 2000;102:61-66.
37. Andreas S, Clemens C, Sandholzer H, Figulla HR, Kreuzer H. Improvement of exercise capacity with treatment of Cheyne-Stokes respiration in patients with congestive heart failure. J Am Coll Cardiol 1996;27:1486-1490.
38. Franklin KA, Eriksson P, Sahlin C, Lundgren R. Reversal of central sleep apnea with oxygen. Chest 1997;111:163-169.
39. Hanly PJ, Millar TW, Steljes DG, Baert R, Frais MA, Kryger MH. The effect of oxygen on respiration and sleep in patients with congestive heart failure. Ann Intern Med 1989;111:777-782.
40. Staniforth AD, Kinnear WJ, Starling R, Hetmanski DJ, Cowley AJ. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. Eur Heart J 1998;19:922-928.
41. 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;116:1550-1557.
42. Teschler H, Dohring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med 2001;164:614-619.
43. Pepperell JC, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JR, Davies RJ. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. Am J Respir Crit Care Med 2003;168:1109-1114.
44. Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. Am Heart J 2001;142:393-401.
45. Bradley TD, Logan AG, Floras JS. Rationale and design of the Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure patients with Central Sleep Apnea—CANPAP. Can J Cardiol 2001;17:677-684.