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PRO/CON DEBATE

CPAP Should Not Be Used for Central Sleep Apnea in Congestive Heart Failure Patients

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Both sleep apnea and congestive heart failure are common disorders. However, systolic heart failure appears to be the most common cause of central and perhaps obstructive sleep apnea.[1-3] Obstructive sleep apnea is also common in isolated diastolic heart failure and may contribute to the progression of left ventricular remodeling and perhaps play a causative role.[1,3-6] However, prevalence and impact of sleep apnea have been most systematically studied in systolic heart failure, and a number of reports show a high prevalence of both central and obstructive sleep apnea in this disorder.[7-11] It is generally assumed that these disordered breathing events, via neurohormonal stimulation, oxidative stress, and activation of redox-sensitive genes and inflammation, contribute to progressive remodeling of cardiac chambers and eventually to morbidity and mortality of heart failure patients.[1-3,6] If true, treatment of sleep apnea should result in reversal of its pathophysiological consequences and in reverse remodeling of cardiac chambers, and eventually in improvement in morbidity and mortality of patients with heart failure.

Treatment of obstructive sleep apnea in heart failure is generally the same as the treatment of this disorder without heart failure, and application of CPAP is the treatment of choice. Two randomized but short-term (1 to 3 months) studies[12,13] with CPAP showed improved left ventricular ejection fraction in patients who have obstructive sleep apnea with left ventricular systolic dysfunction. However, no long-term mortality studies have been performed. Similarly, in patients with diastolic heart failure, treatment of obstructive sleep apnea with CPAP has resulted in reverse remodeling of ventricular morphology and improved function.[4,5]

In contrast to treatment of obstructive sleep apnea where application of nasal CPAP invariably results in virtual elimination of obstructive disordered breathing events, treatment of central sleep apnea in systolic heart failure is difficult,[1,2,6] and response to therapy could be variable. There are several options including use of positive airway pressure devices, nocturnal administration of oxygen, and medications such as theophylline and acetazolamide.[1-3,6]

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Carefully executed short-term double-blind placebo-controlled trials have been performed with oxygen,[14] theophylline,[15] and acetazolamide.[16] These studies show considerable improvement in sleep apnea and desaturation. Oxygen has been studied most extensively.[17,18] These studies show a decrease in sympathetic activity[19,20] and improvement in left ventricular ejection fraction.[21] However, only CPAP has been subjected to a long-term mortality trial.

Early studies of CPAP to treat central sleep apnea in systolic heart failure showed differing results with a number of trials showing no effects,[22-25] and trials primarily from Toronto showing positive effects.[26,27] One trial also showed worsening of heart failure and death in some patients while on CPAP.[25] In any case, in spite of the early enthusiasm from Toronto studies, the multicenter Canadian trial failed to confirm the initial observations, and the question is why.

In the Canadian multi-center trial[28] of CPAP to treat central sleep apnea, 258 patients were randomized to a control group (n=130) and CPAP (n=128) treatment arm. The average age of 63 years, left ventricular ejection fraction of 25%, apnea-hypopnea index of 40 per hour, and a minimum saturation of 81% were typical features of heart failure patients with periodic breathing and central sleep apnea.[7] These baseline features were similar in the two randomized groups. Patients were adapted to CPAP within the course of 1 to 3 nights (without polysomnography or monitoring routine hemodynamics) and the maximum pressure was set at 10 cm H_2O or whatever was tolerated. A second polysomnogram was performed at 3 months to determine the efficacy of CPAP and further adjustments that needed to be made. Patients who had used CPAP for three months showed a 50% reduction in the apnea-hypopnea index, considerable improvement in desaturation, decreased plasma norepinephrine level, and an increase in left ventricular ejection fraction (all statistically significant). There were no significant differences in the apnea-hypopnea index, norepinephrine levels, and other cardiac variables in the control group. However, the improvement noted in sleep apnea and cardiac parameters in the CPAP arm were not as robust as those in the earlier studies from Toronto.[26] Meanwhile, after the first 200 patients had been followed for a minimum of 6 months and an average follow-up of 2 years, the safety-monitoring committee performed a prespecified interim analysis and recommended termination of the study. This was in part related to an early divergence of the transplantation-free survival (the primary endpoint) curves favoring the control group (p = .02). The curves diverged

after about 3 years favoring CPAP arm but the difference was not statistically significant (p = .06). In addition, it may be argued that treatment with CPAP had resulted in the early mortality of the sickest patients and the late divergence of the 2 survival curves was in part due to the early effects of CPAP on mortality (survival bias).

It is noted that the early divergence in transplantation-free survival in favor of the control group occurred in spite of improvement in periodic breathing and desaturation in the CPAP group when compared to the control arm. It also must be emphasized that the increased mortality was primarily due to the increased number of deaths from progressive heart failure and sudden death. What could be the possible causes of early mortality in CPAP-treated patients? There are several possibilities. 1) Those who died were heart failure patients with central sleep apnea whose periodic breathing was nonresponsive to CPAP. 2) Those that died were heart failure patients whose right ventricular function (according to the Frank-Starling curve) was preload dependent. 3) A similar preload dependency of the left ventricular function could also have accounted for increased mortality. 4) Those that died had severe central sleep apnea, were CPAP-nonresponsive, and for a number of reasons were most affected by its adverse hemodynamic effects. Below I briefly review these issues hoping that future trials may be set with consideration of these potential factors which might have contributed to CPAP-related increased mortality.

As noted, the first follow-up polysomnogram was performed three months after use of CPAP, showing that the average AHI had decreased by about 50% (from 40 to 20 per hour). I was not surprised by this finding. In this regard, although treatment of obstructive sleep apnea with CPAP is generally homogeneous, in that application of nasal CPAP virtually eliminates the obstructive disordered breathing events, it is not commonly known that the response to treatment with CPAP in central sleep apnea is not homogeneous, with some patients being nonresponders. Therefore, although the average apnea hypopnea index decreased, I suggest that in the Canadian study, there were some patients who were CPAP nonresponders, and they were the patients who died early on. The first sleep study on CPAP was performed three months after its use.[28] The authors claimed that the first-night CPAP titration was not performed because during the first night CPAP is ineffective. This is inconsistent with the results of our study[29] in which first-night CPAP titration resulted in virtual elimination of central sleep apnea in 43% of the patients. In these patients, the apnea-hypopnea index decreased from about 36 per hour to 4 per hour, and the central apnea index decreased from 22 per hour to 2 per hour (central apneas accounted for two-thirds of all disordered breathing events). Meanwhile, the 57% of the patients who were CPAP nonresponders characteristically had more severe central sleep apnea (with an apnea-hypopnea index equal to about 60 per hour) and were more hypocapnic (although the latter was not significant) than the CPAP responders. Incidentally, we found a similar trend with treatment with oxygen;[17] oxygen nonresponders had more severe central sleep apnea and were also more hypocapnic than responders. In my opinion, therefore, the results of a first night CPAP trial in the Canadian study could have had value to predict if acute CPAP nonresponders contributed to the excess early mortality. Also, I wonder whether a low $PaCO_2$ would have been predictive of nonresponsiveness as it was suggested by our studies of CPAP and oxygen.[17,29]

However, it is possible to analyze the data obtained in the Canadian study at three months to answer the above question. If this analysis shows that CPAP nonresponders at three months have greater long-term mortality than responders, the finding will confirm my hypothesis. I believe that the CPAP nonresponders at three months were also nonresponders on the first night of the CPAP trial if they had been studied. In other words, it is unlikely that CPAP responders on the first night became nonresponders later on.

The other potential mechanism that could have contributed to the early mortality in the CPAP arm relates to the adverse hemodynamic effects of CPAP. Because CPAP increases intrathoracic pressure, it could adversely affect right and left ventricular stroke volume. Also, depending on the increase in the lung volume, CPAP could increase pulmonary vascular resistance increasing right ventricular afterload. In any case, if right and left ventricular function is preload dependent, any reduction in venous return by the increased intrathoracic pressure could decrease right ventricular stroke volume and return to the left ventricle, decreasing left ventricular stroke volume causing hypotension, diminished coronary blood flow, myocardial ischemia, and arrhythmias. Any such effect of CPAP on blood pressure is further augmented during sleep when blood pressure normally decreases. A consequent low diastolic blood pressure on CPAP during sleep could impair myocardial blood flow particularly in those with elevated ventricular diastolic blood pressure or coronary artery disease. Time of death was not reported in the Canadian trial.

In regard to the right ventricular dysfunction, I must emphasize that there are a number of studies[30-36] showing its importance in predicting mortality of patients with heart failure, particularly in the presence of pulmonary hypertension which increases right ventricular afterload. Right ventricular systolic dysfunction and pulmonary hypertension are common in patients with left ventricular systolic dysfunction and pulmonary hypertension may be severe in patients with severe central sleep apnea.[9] Furthermore, it is conceivable that in the Canadian trial (in contrast to most previous CPAP trials), some patients were prone to adverse hemodynamic effects of CPAP because they were aggressively pharmacologically treated for heart failure. The patients were on a variety of drugs including beta blockers, angiotensin converting enzyme inhibitors, and diuretics (86% on loop diuretics and 34% on spironolactone). If these patients had even borderline intravascular volume depletion, any additional CPAP effect on venous return could have compromised right and left ventricular stroke volume. Administration of other drugs, particularly those with alpha-blocking activity, could further impair venous return in patients on CPAP (it was not mentioned if such drugs were used in the Canadian trial). Another factor that may be important is the presence of atrial fibrillation predisposing patients to adverse hemodynamic effects of CPAP.[37] However, in our acute titration study with CPAP,[29] presence of atrial fibrillation did not appear to result in adverse clinical hemodynamic consequences, and additional analysis of the Canadian trial should be able to address this question.

Collectively, therefore, patients with the most severe central sleep apnea who may have severe pulmonary hypertension, or those with intravascular volume depletion, who at the same time are CPAP nonresponders, are most vulnerable to the adverse hemodynamic effects of CPAP. Such patients could have been the main reason for CPAP-related mortality in the Canadian trial. In

our acute CPAP study[22] using Holter monitoring, we also found that ventricular arrythmias improved only in CPAP-responsive patients. Since in the Canadian trial, sudden death was an important cause of mortality, analysis of Holter data (if available), in relation to CPAP responsiveness is important.

Another question relates to the number of patients enrolled and the study being underpowered. Based on pretrial calculations, 408 patients (204 in each arm) represented the adequate sample size which was calculated based on mortality rates in ACE trials. However, during the trial as beta blockers were administered mortality decreased. This was expected and should have been incorporated in the initial calculation. In any case, in part, because of that, the study became underpowered; yet it must be emphasized that CPAP resulted in excess early mortality which contributed to failure of the trial. I should note that in a previous trial from Toronto ,in which a total of 27 patients were randomized to a CPAP arm and a control group, CPAP treatment resulted in decreased mortality in these compliant patients (p=0.017). In the present Canadian trial there were a total of 408 patients with more than 200 patients in each arm.

In summary, I believe we will learn more valuable lessons through further analysis of the data obtained in the Canadian CPAP trial. Meanwhile, I look forward to a trial with a different positive airway pressure device, i.e., proportional assist adaptive servo-ventilation. This device may be superior to CPAP in being more effective in improving periodic breathing and central sleep apnea,[38-40] having less adverse hemodynamic effect (lower expiratory pressure than CPAP for a given inspiratory pressure), and having better long-term adherence than CPAP.[41] In regard to the latter, in the Canadian trial the average number of hours of daily use of CPAP was 3.6 hours at 1 year and beyond. Meanwhile in studies with positive pressure devices, baseline assessment of right ventricular function, central hemodynamics and volume status, combined with serial hemodynamic monitoring, perhaps as simple as blood pressure, heart rate, and pulse oximetry, particularly during initial application of positive pressure device could prove useful. A first night polysomnography in the laboratory is important,because it may be that the CPAP- nonrespoders are most volunerable to advese hemodynamic effects of positive airway pressure.

I also look forward to long-term trials with other modalities of therapy such as nocturnal nasal supplemental oxygen and drugs such as acetazolamide. Unlike CPAP, these modalities of therapy are obviously not associated with increases in intrathoracic pressure, and in addition may have better adherence. Meanwhile, for now CPAP will sleep alone at night, dreaming for a reunion with Hunter, Cheyne and Stokes.

Finally, I would like to close by congratulating Bradley and colleagues for completing this very important trial with the inherent difficulties of a multi-center study.

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