Role of obstructive sleep apnea on the response to cardiac resynchronization therapy and all-cause mortality

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BACKGROUND The role of obstructive sleep apnea (OSA) on the response to cardiac resynchronization therapy (CRT) and all-cause mortality in patients with advanced heart failure (HF) is unknown.

OBJECTIVE We assessed the association between OSA, response to CRT, and all-cause mortality in patients with HF.

METHODS We analyzed records of 548 consecutive patients (mean age 65 ± 13 years; 216 (39%) women; mean follow-up period 76 ± 17 months) who received a CRT-defibrillator device from January 15, 2007 to March 30, 2016 at our tertiary care referral center.

RESULTS A total of 180 patients (33%) had OSA. Fewer patients in the OSA group (109 [61%]) had improvement in left ventricular ejection fraction (EF) than did those in the non-OSA group (253 [69%]) ($P = .001$). A total of 144 patients (27%) died by the end of follow-up (OSA group: 61 [33%]; non-OSA group 83 [23%]; $P < .001$). OSA diagnosis was associated with a lower chance of improvement in EF (hazard ratio 0.71; 95% confidence interval 0.60–0.89) and a higher risk of all-cause mortality (hazard ratio 3.7; 95% confidence interval 2.5–6.8). This was true in continuous positive airway pressure–compliant patients and in patients with nonischemic cardiomyopathy. However, among patients with ischemic cardiomyopathy, the chance of improvement in EF and all-cause mortality was similar in patients with OSA and those without OSA.

CONCLUSION OSA is associated with a decreased response to CRT and an increase in all-cause mortality in patients with HF. The differential effect of OSA on CRT response in patients with ischemic cardiomyopathy and nonischemic cardiomyopathy needs further study.

KEYWORDS Cardiac resynchronization therapy; Ejection fraction; Heart failure; Mortality; Obstructive sleep apnea

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Introduction

Cardiac resynchronization therapy (CRT) improves outcomes in patients with advanced heart failure (HF).[1,2] However, 30%–40% of patients receiving CRT have suboptimal response and hence have increased risk of HF progression and subsequent mortality.[3–5] As a result, there is considerable interest in elucidating factors associated with nonresponse to CRT. Obstructive sleep apnea (OSA) is prevalent in >35% of patients with HF.[6] OSA favors HF progression.[7–10] However, the role of OSA on the nonresponse to CRT and all-cause mortality in patients with HF is not known.

In order to bridge this literature gap, we performed a retrospective cohort analysis involving patients who received CRT in our tertiary care institution and assessed the association of OSA with nonresponse to CRT and all-cause mortality.

Methods

Study setting and design

The institutional review board of the University of Iowa approved the study. Case records of 675 consecutive patients

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who were initiated on CRT from January 2007 to March 2016 in our tertiary care center were reviewed. Patients were included in the study if (1) they received a CRT-defibrillator device, (2) had chronic systolic HF with a baseline ejection fraction [EF] of <35%, and (3) had New York Heart Association class II, class III, or ambulatory class IV symptoms. In an attempt to maintain homogeneity of the study population, we excluded patients who received a CRT-pacing device (n = 76) and those who received CRT for the indication of reducing right ventricular pacing among patients who had an indication for dual-chamber pacing (n = 51). So in total, 548 patients formed the study cohort.

Baseline data collection

Demographic variables comorbid medical conditions, body mass index, electrocardiographic variables (presence of typical left bundle branch block [LBBB] and QRS complex duration), and EF at the time of CRT initiation and medication use were abstracted by review of medical records. EF assessment was done using Simpson's biplane method of discs.

Cohort, exposure, follow-up, and outcome definition

OSA was the exposure of interest. It is the policy of the HF program in our institution to test for OSA in all patients with advanced HF using a polysomnographic study (sleep study). OSA diagnosis was determined if the case records had a documented polysomnographic study (sleep study) that confirmed the diagnosis of OSA or if the patient used continuous positive airway pressure (CPAP) and the indication for CPAP use was documented to be for OSA. We used the *International Classification of Sleep Disorders* criteria to define OSA.[11] As per this definition, since all patients in our study had a diagnosis of congestive HF, an apnea-hypopnea index (AHI) of ≥5 events/h of sleep, assessed in the baseline sleep study, was suffice to have a diagnosis of OSA. Furthermore, study participants were categorized to have mild, moderate, and severe OSA if they had an AHI between 5 and 15, between 15 and 30, and >30 events/h of sleep, respectively, in the baseline sleep study. CPAP compliance was determined by assessing the CPAP follow-up notes in the patient's medical records. A patient was determined to be compliant with CPAP if the CPAP device interrogation showed that the device was used for at least 4 h/night for at least 70% of nights during a consecutive 30-day period anytime during the first 3 months of initial use and in the 3 months before the last CPAP follow-up visit date that was available before the death of the patient. We chose the above criteria for CPAP compliance because these are the cutoffs used by the Centers for Medicare and Medicaid Services to define CPAP compliance for reimbursement determination.[12] Also, the study by McEvoy et al[13] showed that CPAP use for at least 4 h/night was associated with improved outcomes in patients with OSA. Central sleep apnea (CSA) is an important confounder in our study because CSA increases risk of mortality in these patients.[14] We assessed CSA from the sleep study that was used to ascertain OSA diagnosis at baseline as mentioned above. CSA was diagnosed if the sleep study showed ≥5 central apneas/h of sleep with or without crescendo-decrescendo breathing with a cycle length of at least 40 seconds (ie, Cheyne-Stokes breathing pattern).[14] Our study cohort was open with regard to entry and exit. Participants entered the cohort when CRT-defibrillator therapy was initiated. Their follow-up time started upon entry into the cohort. Their follow-up was censored either if they died, received a left ventricular assist device, or received a heart transplant or upon study conclusion. The outcomes of interest for our study were improvement in EF and all-cause mortality. Patients were considered CRT responders if they had an absolute EF improvement of ≥10% (determined using Simpson's biplane method of discs) compared to baseline on the transthoracic echocardiogram that was assessed before study conclusion or before the death of the patient. Patients who had <10% absolute improvement in EF were referred to as CRT nonresponders. All-cause mortality was determined if mentioned in the case records whether death happened at our institution or by assessing the social security database whether death had happened outside our institution. The biventricular (BiV) pacing percentage was determined at the first follow-up visit after CRT initiation and at the follow-up visit immediately before the death of the patient or before study conclusion.

Statistical analysis

We divided the study cohort into those with OSA (OSA group) and those without OSA (non-OSA group). In each group, continuous variables were expressed as mean ± SD and categorical variables as number (percentage). The 2 groups were then compared with each other using the Student *t* test or the χ^2 test, as appropriate. Then, in order to assess the association between OSA, improvement in EF, and all-cause mortality, we used Cox proportional hazards regression models using time to improvement in EF and time to all-cause mortality as dependent variables and OSA diagnosis as an independent variable. We first assessed the unadjusted association between OSA diagnosis and the study outcomes. Then, we assessed the adjusted association between OSA diagnosis and the study outcomes. Age, sex, obesity, atrial fibrillation diagnosis, OSA severity (coded as a categorical variable: mild, moderate, and severe), presence of typical LBBB, QRS complex duration >150 ms, BiV pacing >90% (assessed at the CRT follow-up visit immediately before the death of the patient or before study conclusion—coded as a categorical variable: yes/no), and CSA diagnosis were the variables adjusted in this model. The variables were selected using the forward selection process on the basis of their significant univariate association with the study outcomes. The criterion was set at $P < .05$. In spite of not being significantly associated with the study outcomes in univariate analysis, sex and presence of LBBB were forced into the models because of prior data that indicated that these

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