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

Introduction
Cardiac resynchronization therapy (CRT) improves outcomes in patients with advanced heart failure (HF). However, 30–40% of patients receiving CRT have suboptimal response and hence have increased risk of HF progression and subsequent mortality. 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. OSA favors HF progression. 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...
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 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 al13 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 χ² 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
variables predicts outcome in patients receiving CRT. The goodness of fit of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test. Then, we performed the adjusted analysis in 2 subgroups: (1) patients with a diagnosis of ischemic cardiomyopathy (ICM) and (2) patients with a diagnosis of nonischemic cardiomyopathy (NICM). Subsequently, we performed a sensitivity analysis assessing the effect of CPAP compliance on the association between OSA and the study outcomes. This model restricted the analysis sample to those patients with OSA who were compliant with CPAP. All analyses were performed using STATA statistical software (STATA 12, Houston, TX). A P value of <.05 was considered statistically significant.

### Results

Of the 548 study cohort participants, 180 (33%) formed the OSA group and 368 (67%) formed the non-OSA group. A comparison of demographic characteristics between the 2 groups is shown in Table 1. The mean baseline AHI in the OSA group was 26 ± 16 events/h of sleep. Eighty-two participants in the OSA group (46%) had severe OSA, 66 (36%) had moderate OSA, and 32 (18%) had mild OSA. Participants in the OSA group were older and had a higher body mass index. A higher proportion of patients in the OSA group had AF and ICM. A higher proportion of patients in the OSA group had a baseline QRS duration of >150 ms and were BiV paced >90% at baseline compared with those in the non-OSA group. However, a higher proportion of patients in the non-OSA group had CSA compared with those in the OSA group at baseline (Table 1). Medication use and baseline EF were mostly similar in the 2 groups at baseline.

The mean follow-up period was 76 ± 17 months for the study cohort (78 ± 14 months for the OSA group and 74 ± 15 months for the non-OSA group; P = .506). A total of 105 patients (58%) were compliant with CPAP in the OSA group. Only 37 among them used CPAP for >5 h/night. The mean AHI by the end of follow-up in CPAP-compliant and noncompliant participants in the OSA group was 3 ± 1 and 22 ± 10 events/h of sleep, respectively. The proportion of patients who were BiV paced >90% did not change significantly by the end of follow-up relative to baseline in the OSA group (baseline: 87% vs end of follow-up: 85%; P = .36) and the non-OSA group (baseline: 81% vs end of follow-up: 83%; P = .36). EF remained unchanged in the OSA group by the end of follow-up (baseline: 28% ± 5% vs end of follow-up: 27% ± 7%; P = .71), whereas the non-OSA group improved their EF by the end of follow-up (baseline: 27% ± 6% vs end of follow-up: 45% ± 7%; P < .001). The OSA group had a higher mean number of HF hospitalizations (OSA group: 4 ± 1; non-OSA group: 2 ± 1). Furthermore, the OSA group had higher LV end-diastolic dimensions (OSA group: 6.4 ± 1.0 cm; non-OSA group: 6.1 ± 0.6 cm) and LV end-systolic volume index (OSA group: 42 ± 4 mL/m²; non-OSA group: 33 ± 4 mL/m²) by the end of follow-up.

By the end of follow-up, 362 (66%) in the study cohort had improvement in EF. However, when the 2 groups were compared, a significantly lower proportion of patients in

### Table 1  Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total cohort (N = 548)</th>
<th>OSA group (n = 180)</th>
<th>Non-OSA group (n = 368)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65 ± 13</td>
<td>70 ± 11</td>
<td>63 ± 13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex: female</td>
<td>216 (39.4)</td>
<td>72 (40)</td>
<td>144 (39)</td>
<td>.860</td>
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<tr>
<td>Caucasians</td>
<td>443 (81)</td>
<td>149 (83)</td>
<td>294 (80)</td>
<td>.112</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 5</td>
<td>33 ± 3</td>
<td>24 ± 6</td>
<td>.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>131 (24)</td>
<td>61 (34)</td>
<td>70 (19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes diagnosis</td>
<td>180 (33)</td>
<td>68 (38)</td>
<td>112 (30)</td>
<td>.086</td>
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<tr>
<td>Hypertension diagnosis</td>
<td>378 (69)</td>
<td>128 (71)</td>
<td>250 (68)</td>
<td>.100</td>
</tr>
<tr>
<td>Atrial fibrillation diagnosis</td>
<td>148 (27)</td>
<td>70 (39)</td>
<td>78 (22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Typical LBBB</td>
<td>330 (60)</td>
<td>111 (62)</td>
<td>219 (60)</td>
<td>.628</td>
</tr>
<tr>
<td>QRS duration &gt;150 ms</td>
<td>367 (67)</td>
<td>124 (70)</td>
<td>243 (65)</td>
<td>.048</td>
</tr>
<tr>
<td>CKD</td>
<td>136 (25)</td>
<td>46 (26)</td>
<td>90 (24)</td>
<td>.780</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>88 (16)</td>
<td>31 (16)</td>
<td>57 (15)</td>
<td>.455</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>224 (41)</td>
<td>104 (58)</td>
<td>120 (33)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
<td>324 (59)</td>
<td>76 (42)</td>
<td>248 (67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Central sleep apnea at baseline</td>
<td>126 (23)</td>
<td>25 (14)</td>
<td>101 (27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline ejection fraction (%)</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
<td>27 ± 6</td>
<td>.311</td>
</tr>
<tr>
<td>BiV paced &gt;90%</td>
<td>454 (83)</td>
<td>157 (87)</td>
<td>297 (81)</td>
<td>.047</td>
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<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>β-Blockers</td>
<td>443 (81)</td>
<td>144 (80)</td>
<td>299 (81)</td>
<td>.201</td>
</tr>
<tr>
<td>ACEs/ARBs</td>
<td>427 (78)</td>
<td>144 (80)</td>
<td>283 (77)</td>
<td>.199</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>224 (41)</td>
<td>70 (39)</td>
<td>154 (42)</td>
<td>.137</td>
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<td>Warfarin</td>
<td>115 (21)</td>
<td>38 (21)</td>
<td>77 (20)</td>
<td>.311</td>
</tr>
<tr>
<td>Non–vitamin K oral anticoagulants</td>
<td>55 (10)</td>
<td>20 (11)</td>
<td>35 (10)</td>
<td>.192</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>361 (66)</td>
<td>117 (65)</td>
<td>244 (66)</td>
<td>.388</td>
</tr>
<tr>
<td>Clopidogrel use</td>
<td>126 (23)</td>
<td>45 (25)</td>
<td>81 (22)</td>
<td>.109</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or as n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BiV = biventricular; BMI = body mass index; CKD = chronic kidney disease; LBBB = left bundle branch; OSA = obstructive sleep apnea.
the OSA group (109 [61%]) had improvement in EF [109 (61%)] compared with those in the non-OSA group (253 [69%]) \((P = .001)\). Furthermore, in the OSA group, a lower proportion of patients in the severe OSA group (40 [49%]) improved their EF compared with those in the moderate (44 [66%]) and mild (25 [78%]) OSA groups \((P < .001)\). OSA diagnosis was associated with a lower chance of improvement in EF in the unadjusted and adjusted models (Table 2). Of note, adjustment for OSA severity did not alter the lower chance of improvement in EF in patients with OSA (Table 2). In the sensitivity analysis, when restricted to CPAP-compliant patients in the OSA group, the association between OSA and all-cause mortality remained significant (Table 2). In the subgroup analysis involving patients with NICM, 73 died (23%) by the end of follow-up (OSA group: 30 [39%]; non-OSA group: 43 [17%]; \(P < .001\)). OSA significantly increased risk of all-cause mortality in this subgroup of patients in the unadjusted and adjusted models (Table 2). Figure 2 shows the unadjusted survival curves comparing the OSA group with the non-OSA group among patients with NICM. In the subgroup analysis involving patients with ICM (n = 224), 71 died by the end of follow-up (OSA group: 31 [30%]; non-OSA group: 40 [33%]; \(P = .089\)). Figure 3 shows the unadjusted survival curves comparing the OSA group with the non-OSA group among patients with ICM. The risk of all-cause mortality was similar in the OSA group and the non-OSA group among this subgroup in the unadjusted and adjusted models (Table 2).

### Discussion

In this retrospective cohort analysis, we report higher rates of nonresponse to CRT and all-cause mortality in CRT recipients with OSA than in those without OSA. This effect was primarily seen in patients with NICM, while presence of OSA was not a significant predictor of CRT nonresponse or mortality in patients with ICM.

By increasing ventricular preload and afterload, OSA reduces stroke volume and overall cardiac function. This leads to cardiac hypertrophy and cardiomyocyte apoptosis.\(^2\),\(^15\) Furthermore, OSA results in a state of sympathetic excess with exaggerated neurohumoral activation and resultant salt and water retention.\(^16\),\(^17\) OSA as a predictor of nonresponse to CRT has not been reported...
in the literature, and ours appears to be the first study to report this association. LBBB, sex, AF diagnosis, BiV pacing percentage, and a wider QRS duration are known variables associated with CRT response. Hence, LBBB and sex were forced into the adjusted Cox models since we sought to assess the association of OSA and the study outcomes, independent of known prognostic indicators of CRT response. The association of OSA with CRT nonresponse and all-cause mortality in our study remained independent and strong in spite of adjustment for these known factors associated with CRT response. In addition, CSA (a known poor prognostic marker in HF) failed to alter the association between OSA, CRT nonresponse, and mortality.

The mechanism underlying the association of OSA with an increased risk of nonresponse to CRT and all-cause mortality is unclear. However, the association between CRT response and change in OSA severity has been studied. Stanchina et al showed that after effective CRT, their study participants with OSA improved their EF, improved cardiac output, and subsequently improved their AHI. It was inferred that an improvement in cardiac output resulted in better perfusion and a reduction in circulation time. This so-called ventilator loop theory postulates that these hemodynamic improvements result in synonymous perfusion to the ventilator chest muscles and the ventilator centers in the brain, thereby resulting in synchronous functioning of these 2 elements and a resultant decrease in AHI. In corollary, our study CRT recipients with OSA probably had poorer cardiac output at the time of CRT initiation by virtue of low EF and the pathobiology of OSA as discussed above. They may have entered an unfavorable feedback loop with the low cardiac output worsening OSA, and vice versa; this in turn may have driven a poor CRT response and subsequent increased mortality risk. Confirming this hypothesis is beyond the scope of our research because we lacked objective hemodynamic data including cardiac output assessment.

CPAP compliance did not nullify the association between OSA and all-cause mortality in our study. Since CPAP use is known to improve quality of life, sicker and more symptomatic participants with OSA in our study may have been compliant to CPAP but still could have experienced poorer outcomes because of their baseline poor state of health. Evidence is conflicting with regard to the benefit of CPAP in the treatment of OSA of patients with HF. CPAP use is known to reduce systolic blood pressure and improve LV systolic function in patients with HF. However, a recent large meta-analysis that pooled data from 7 randomized studies showed that although CPAP use for 3.5 h/d significantly reduced the risk of major adverse cardiac events, it did not have any benefit in reducing HF and all-cause mortality specifically. However, the sensitivity analysis in this study did suggest the possibility that longer duration of CPAP use may potentially improve HF and mortality outcomes. Because of limited power of our study with only 37 of our patients using CPAP for 5 h/night, we were unable to assess whether longer duration of CPAP use will improve CRT response. Hence, randomized trials of CPAP use on CRT outcomes are needed to assess whether longer duration of CPAP use will positively influence CRT response in patients with OSA.

Finally, the differential effect of OSA in patients with ICM and NICM (Figures 2 and 3) is a novel finding and may have implications for CRT in patients with NICM. Prior evidence has shown that CRT response rates are higher in patients with NICM than in those with ICM. We observed that OSA was a predictor of poor CRT response and all-cause mortality in patients with NICM and not in patients with ICM. This could just be a finding by chance or the lack of adequate power to detect a difference in patients with ICM. Hence, randomized trials of intensive OSA therapy are needed in patients with ICM and NICM who are undergoing CRT.

**Figure 2** Association between OSA and all-cause mortality in patients with ICM. Survival curves comparing all-cause mortality outcome between the OSA group and the non-OSA group among patients with ICM. ICM = ischemic cardiomyopathy; OSA = obstructive sleep apnea.

**Figure 3** Association between OSA and all-cause mortality in patients with NICM. Survival curves comparing all-cause mortality outcome between the OSA group and the non-OSA group among patients with NICM. NICM = nonischemic cardiomyopathy; OSA = obstructive sleep apnea.
Study limitations
Although we had granular data with regard to patient characteristics and follow-up and used objective OSA definition that potentially reduced exposure misclassification, our analysis did have important limitations. Ours was a single-center study, and hence study center characteristics could have biased the results. Also, we assessed time to improvement in EF by the follow-up time between study entry to when the final transthoracic echocardiogram was performed, which may not necessarily be the exact time when participants improved their EF. Because this is a retrospective cohort analysis, we were limited in our ability to assess EF at closer intervals to capture the exact time to improvement in EF. Furthermore, although we used a relatively large sample of CRT recipients, wide confidence intervals of our effect estimates are evidence that we probably lacked precision. Hence, it is worthwhile to repeat our analysis with larger CRT registries. Also, surveillance bias is possible with closer follow-up offered to CRT nonresponders. This could have tipped the effect estimate toward a null association, but in spite of this we noted a strong association between OSA and all-cause mortality.

Conclusion
OSA is a predictor of nonresponse to CRT and increases risk of mortality in patients with HF. This is especially true in patients with NICM. Screening for OSA in CRT recipients may identify those at risk for nonresponse to CRT. The effect of CPAP on CRT response in patients with OSA and HF needs to be tested in randomized studies.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hjrtm.2018.06.016.

References