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SCIENTIFIC INVESTIGATIONS

Sleep apnea and recurrent heart failure hospitalizations after coronary artery bypass grafting

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Study Objectives: Sleep apnea is prevalent in patients undergoing coronary artery bypass grafting (CABG). We investigated the relationship between sleep apnea and recurrent heart failure hospitalizations in patients undergoing nonurgent CABG.

Methods: Between November 2013 and December 2018, 1,007 patients completed a sleep study prior to CABG and were followed up until April 2020. Recurrent heart failure hospitalizations were analyzed by Poisson, negative binomial, Andersen–Gill, and joint frailty models, with partial and full adjustment for covariates.

Results: At an average follow-up of 3.3 years, the number of patients with 0, 1, or ≥ 2 heart failure hospitalizations were 908 (90.2%), 62 (6.2%), and 37 (3.7%), respectively. The total number of heart failure hospitalizations was 179, comprising 62 (35%) first and 117 (65%) repeat events. The numbers of heart failure hospitalizations for the sleep apnea (n = 513, 50.9%) and nonsleep apnea groups were 127 and 52, respectively. Negative binomial regression demonstrated that sleep apnea was associated with recurrent heart failure hospitalizations (fully adjusted rate ratio, 1.71; 95% confidence interval [CI], 1.12–2.62; $P = .013$). Similar results were found in Poisson (1.63; 95% CI, 1.15–2.31; $P = .006$), Andersen–Gill (1.66; 95% CI, 1.01–2.75; $P = .047$), and joint frailty models (1.72; 95% CI, 1.00–3.01; $P = .056$)

Conclusions: In patients after CABG, repeat events accounted for two-thirds of heart failure hospitalizations. Sleep apnea was independently associated with recurrent heart failure hospitalizations.

Keywords: sleep, coronary artery bypass grafting, heart failure, statistics

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep apnea is prevalent in patients undergoing coronary artery bypass grafting. We investigated the relationship between sleep apnea and recurrent heart failure hospitalizations in patients undergoing nonurgent coronary artery bypass grafting.

Study Impact: In patients after coronary artery bypass grafting, repeat events accounted for two-thirds of heart failure hospitalizations. Sleep apnea was independently associated with recurrent heart failure hospitalizations.

INTRODUCTION

Coronary artery bypass grafting (CABG) is the most common cardiac surgery worldwide. In the United States alone, the annual volume of CABG procedures is over 150,000.[1] Although adjunctive pharmacotherapy and technical advances have reduced the perioperative mortality to 1–3%,[2,3] the incidence of unscheduled hospitalizations within the first year after CABG is up to 40%.[4,5] Unscheduled hospitalizations result in compromised satisfaction and financial burden on both patients and institutions.[5,6] Notably, a leading cause of unscheduled hospitalizations after CABG is heart failure.[4,5]

Sleep apnea is a prevalent comorbidity in patients with cardiovascular disease and occurs in approximately 50% of patients undergoing CABG.[7,8] Characterized by repetitive episodes of upper-airway obstruction during sleep, which result in intermittent hypoxia and sleep arousal,[9,10] sleep apnea is associated with adverse myocardial remodeling[11] and decreased survival in patients with stable heart failure.[12] In the recently published Sleep Apnea and Bypass Operation (SABOT) study, we showed that at 2 years after a nonemergent CABG patients with sleep apnea had a 1.57-fold increased risk of having a composite endpoint that comprised cardiac death, myocardial infarction, stroke, and unplanned revascularization.[13] However, that analysis was based on conventional time-to-first-event analysis, which is suboptimal for heart failure hospitalization as data on repeat events are ignored.[14] Because heart failure hospitalization is an endpoint that recurs frequently, the use of repeat-event analysis provides a better representation of disease burden than time-to-first-event analysis.[15–18]

To address this issue, we conducted a secondary analysis of the extended follow-up data of the SABOT study to investigate the association between sleep apnea and recurrent heart failure hospitalizations in patients undergoing a nonemergent CABG. As there is no universal expert consensus regarding the optimal method,[19] we used four widely used statistical models for recurrent heart

failure hospitalizations, namely the Poisson regression, Andersen–Gill, negative binomial regression, and joint frailty models.[15–18] We hypothesized that the burden of recurrent heart failure hospitalizations would be higher in the sleep apnea group than in the nonsleep apnea group.

METHODS

Study design

The study design and results of the SABOT study have been published elsewhere.[13] The SABOT study was a prospective observational cohort study of patients undergoing nonemergent CABG that investigated the association between sleep apnea and the primary composite endpoint of major adverse cardiac and cerebrovascular events, including cardiac death, myocardial infarction, stroke, and unplanned revascularization (the main findings were not repeated in this report). The analyses of the endpoints were based on time-to-first-event using Cox proportional hazards regression. The SABOT study complies with the Declaration of Helsinki and has been registered with ClinicalTrials.gov (NCT02701504) and was approved by the local institutional review board (Domain Specific Review Board-C, National Healthcare Group Reference number: DSRB-C: 2013/00570). All participants gave written informed consent. The data underlying this article will be shared on reasonable request to the corresponding author.

During the study period, sleep apnea screening and treatment before CABG was not a standard clinical practice at our institution. Patients aged 18–90 years who were scheduled to undergo nonemergent CABG, defined as an interval of > 24 hours between the decision to perform CABG and the operative procedure, were deemed eligible for this study. Patients were excluded if they had received continuous positive airway pressure therapy or other forms of treatment for sleep apnea, mechanical ventilation or an intraaortic balloon pump for cardiogenic shock, or oxygen therapy for an exacerbation of ongoing heart failure; were considered high-risk for malignant arrhythmia; were using long-term α-blocker therapy; or had a history of severe chronic pulmonary disease. As a standard practice at our institution, all patients undergoing nonemergent CABG were admitted at least 1 day prior to surgery. Eligible patients underwent an overnight sleep study on the night before CABG. The teams providing clinical care to the patients were blinded to the results of the sleep study. All patients were followed prospectively via a combination of clinic visits, medical records review, and/or telephone contact. All subsequent clinical care and management was conducted as per routine clinical practices. Out of the 1,378 patients approached, 272 declined participation. This is an ancillary study of the original SABOT study, and a CONSORT diagram is available in the original publication.[13]

Sleep apnea is defined as an apnea-hypopnea index of ≥ 15 events/h. All patients were followed prospectively through a combination of clinical visits, electronic records review, and/or phone contact.

Between November 2013 and December 2018, a total of 1,007 patients were recruited and underwent a sleep study (prior to administration of sedation or anesthesia) using a US Food and Drug Administration–approved wrist-worn portable device (Watch-PAT 200, Itamar Medical, Caesarea, Israel). Sleep apnea was diagnosed in 513 (50.9%, out of 1,007) patients. All of the study participants who underwent a sleep study were informed of the results by mail within 1 month. Patients diagnosed with sleep apnea were offered a referral letter to the sleep clinic for evaluation. Only six patients accepted the referral and three attended the sleep clinic. None of the three patients was on continuous positive airway pressure therapy for more than 3 months.

Heart failure hospitalization

Heart failure hospitalization was predefined as an unscheduled hospital admission for a primary diagnosis of heart failure with a length of stay exceeding 24 hours, according to the 2017 Standardized Data Collection for Cardiovascular Trials Initiative.[20] As a standard practice at our institution, all patients admitted for heart failure after CABG underwent an echocardiography. All the echocardiography studies were analyzed at the same laboratory. For this report, left ventricular ejection fraction was categorized into reduced (< 50%) vs preserved (≥ 50%).

Statistical analysis

Bar plots were used to illustrate the distribution of heart failure hospitalizations between the sleep apnea and nonsleep apnea groups. The cumulative incidence of heart failure hospitalizations and its rate ratio were calculated for the two groups.

Frequencies and percentages were used to summarize the categorical variables, and Pearson's χ^2 test for independence was used to compare the categorical variables among the groups based on the number of heart failure hospitalizations (ie, 0, 1, and ≥ 2). Continuous variables following normal distributions were presented as means with standard deviations and compared using one-way analysis of variance. Variables that did not follow normal distributions were summarized as medians with interquartile ranges and compared using Kruskal–Wallis one-way analysis of variance.

All patients were followed up prospectively for an extended duration until April 30, 2020. To account for the heart failure hospitalizations in the extended follow-up duration, Cox regression time-to-first-event analysis was conducted.

Four recurrent analyses of heart failure hospitalizations were performed, taking into account the total exposure time of each patient. These analyses are widely adopted across a range of approaches.[18,21,22] In the Poisson regression model, the rate ratio for heart failure hospitalizations between the sleep apnea and nonsleep apnea groups was derived.[22] However, as the recurrence of heart failure hospitalizations is associated with individual patient factors, this violates the assumption of Poisson regression that the likelihood of recurrent heart failure hospitalizations is similar across patients. Hence, negative binomial regression was additionally utilized, which models the recurrent events of each patient according to his/her own Poisson hospitalization rate, thus inducing an association between recurrent events.[16,18] As the time between recurrent events is not accounted for in the Poisson regression and negative binomial regression models, the Andersen–Gill model was additionally utilized.[18,21] Robust standard errors were used in the Andersen–Gill model to account for

heterogeneity in heart failure hospitalizations within patients.[21,22]

To account for the competing risk of cardiovascular death, a composite of heart failure hospitalizations and cardiovascular deaths was computed to derive adjusted rate ratios in the Poisson and negative binomial regressions.[16,18] Additionally, the joint frailty model was utilized as the fourth model in our analyses, as it simultaneously analyses heart failure hospitalizations and an associated time to cardiovascular death.[18]

Two multivariate models were built using baseline covariates with statistically significant association with heart failure hospitalizations ($P < .05$) and based on clinical relevance. Adjusted rate ratios were calculated for all statistical analyses.

Descriptive statistics and the majority of recurrent analyses were carried out using the IBM SPSS Statistics 25 (IBM, New York, New York, United States). The Andersen–Gill models fitted using the Lin–Wei–Yang–Ying semiparametric regression approach were computed using the "reReg" package,[23] while the joint frailty models were fitted using the "frailtypack" package[24] in the R software (version 3.5.2; The R Project for Statistical Computing, Vienna, Austria). A statistically significant finding was indicated by a two-sided P value of $< .05$.

RESULTS

Incidence of heart failure hospitalizations

The average follow-up duration was 3.3 ± 2.4 years. Out of the 1,007 patients, 68 died and the numbers of patients with 0, 1, or ≥ 2 heart failure hospitalizations were 908 (90.2%), 62 (6.2%), and 37 (3.7%), respectively. The maximum number of heart failure hospitalizations per patient was 11. Among the 99 patients with at least 1 heart failure hospitalization, 62 had reduced (< 50%) and 37 had preserved (≥ 50%) left ventricular ejection fraction based on echocardiography. The total number of heart failure hospitalizations was 179, 62 (35%) of which were first events and 117 (65%) were repeat events. No association was observed between the left ventricular ejection fraction (< 50% vs ≥ 50%) and the number of heart failure hospitalizations ($P = .584$).

The average follow-up durations were similar between the sleep apnea (n = 513) and nonsleep apnea (n = 494) groups (3.3 ± 3.1 vs 3.4 ± 1.5 years, $P = .467$). The numbers of heart failure hospitalizations in the sleep apnea and nonsleep apnea groups are compared in **Figure 1**. The total cost of heart failure hospitalizations for the sleep apnea and nonsleep apnea groups was $679,535 and $278,235, respectively.

Baseline variables and heart failure hospitalizations

The baseline demographic and clinical characteristics of the patients with 0, 1, or ≥ 2 heart failure hospitalizations are shown in **Table 1**. Compared with patients without heart failure hospitalizations, those with heart failure hospitalizations (1 or ≥ 2) were older, more likely to be Indians (vs Chinese and Malays), had higher prevalence of hypertension and diabetes mellitus, and were more likely to have a family history of premature coronary artery disease. Likewise, compared with patients without or with 1 heart failure hospitalization, patients with ≥ 2 heart failure hospitalizations had a higher prevalence of chronic kidney disease, previous myocardial infarction, previous percutaneous coronary intervention, higher apnea-hypopnea index, higher oxygen desaturation index, and higher percentage of sleep with arterial oxygen saturation < 90%.

Table 2 presents the findings from the diagnostic coronary angiography and echocardiography evaluation. Compared with patients without or with 1 heart failure hospitalization, patients with ≥ 2 heart failure hospitalizations were more likely to have

Figure 1—Number of heart failure hospitalizations by sleep apnea status.

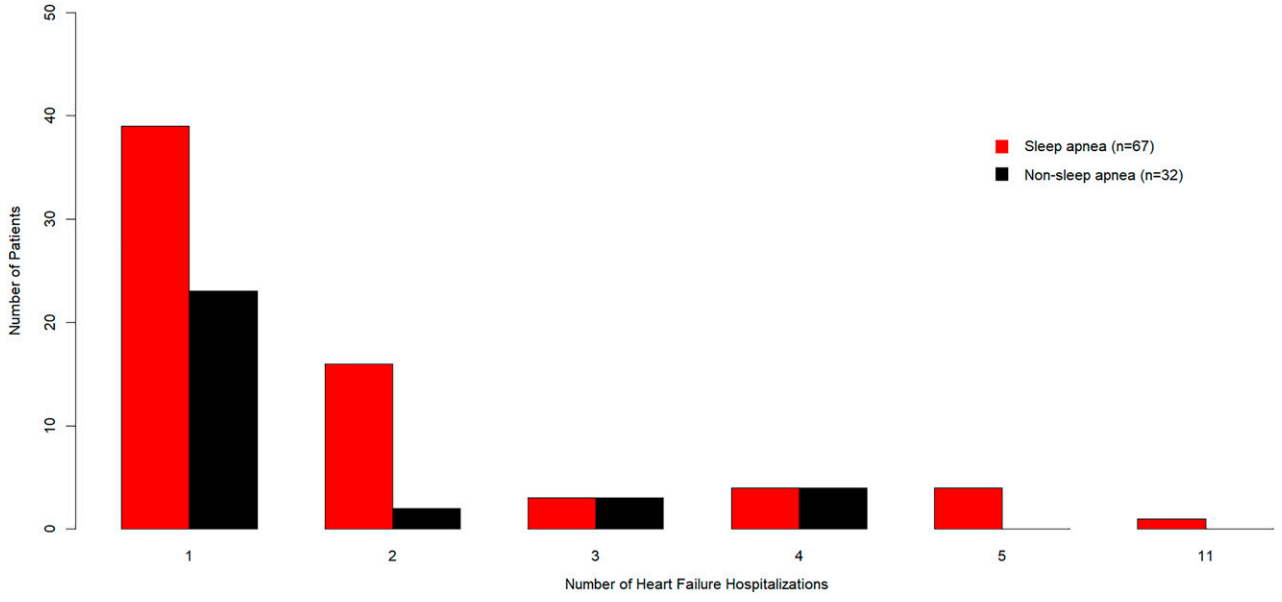

Table 1—Demographic, clinical characteristics, and sleep study results.

Characteristics	Number of Heart Failure Hospitalizations			*P*
	0 (n = 908)	1 (n = 62)	≥ 2 (n = 37)	
Age, median (IQR), y	61.0 (56–67)	65.5 (58.8–69.3)	62.0 (56.5–69.5)	.026
Male sex, n (%)	789 (86.9)	51 (82.3)	31 (83.8)	.520
Ethnicity, n (%)				.008
Chinese	597 (65.7)	36 (58.1)	19 (51.4)	
Malay	178 (19.6)	10 (16.1)	6 (16.2)	
Indian	85 (9.4)	12 (19.4)	10 (27.0)	
Others	48 (5.3)	4 (6.5)	2 (5.4)	
Clinical measurements				
Systolic blood pressure, mean (SD), mm Hg	126 (19)	125 (18)	124 (21)	.756
Diastolic blood pressure, mean (SD), mm Hg	71 (11)	69 (11)	67 (9)	.016
Body mass index, mean (SD), kg/m^2	25.2 (4.0)	25.0 (4.2)	26.0 (5.1)	.477
Neck circumference, mean (SD), cm	38.5 (3.3)	38.7 (3.6)	38.9 (3.7)	.821
Waist circumference, mean (SD), cm	93.1 (10.6)	94.3 (11.1)	96.0 (13.2)	.209
Cardiovascular risk factors, n (%)				
Smoking status				.958
Nonsmoker	456 (50.2)	34 (54.8)	19 (51.4)	
Ex-smoker	268 (29.5)	16 (25.8)	10 (27.0)	
Current smoker	184 (20.3)	12 (19.4)	8 (21.6)	
Hyperlipidemia	730 (80.4)	55 (88.7)	33 (89.2)	.121
Hypertension	668 (73.6)	53 (85.5)	32 (86.5)	.028
Diabetes mellitus	493 (54.3)	49 (79.0)	31 (83.8)	<.001
Family history of premature coronary disease	239 (26.3)	28 (45.2)	14 (37.8)	.002
Concomitant conditions, n (%)				
Previous myocardial infarction	404 (44.5)	30 (48.4)	26 (70.3)	.008
Previous percutaneous coronary intervention	191 (21.0)	14 (22.6)	15 (40.5)	.019
Previous coronary artery bypass surgery	2 (0.2)	0 (0.0)	0 (0.0)	.897
Preexisting heart failure	44 (4.8%)	12 (19.4%)	10 (27.0%)	<.001
Stroke/transient ischemic attack	107 (11.8)	5 (8.1)	6 (16.2)	.466
Chronic kidney disease[a]	137 (15.1)	13 (21.0)	15 (40.5)	<.001
Chronic kidney disease on dialysis	30 (3.3)	2 (3.2)	4 (10.8)	.054
Preexisting atrial fibrillation	43 (4.7)	3 (4.8)	1 (2.7)	.846
Pacemaker in situ	2 (0.2)	0 (0.0)	1 (2.7)	.023
Implantable cardioverter defibrillator in-situ	4 (0.4)	0 (0.0)	0 (0.0)	.803
Sleep study results				
AHI, events/h, median (IQR)	14.5 (5.7–28.9)	19.7 (9.0–37.9)	35.3 (16.7–53.6)	<.001
No sleep apnea (AHI < 5)	193 (21.3%)	10 (16.1%)	4 (10.8%)	<.001
Mild sleep apnea (AHI 5 to < 15)	269 (29.6%)	13 (21.0%)	5 (13.5%)	
Moderate sleep apnea (AHI 15 to < 30)	230 (25.3%)	17 (27.4%)	7 (18.9%)	
Severe sleep apnea (AHI ≥ 30)	216 (23.8%)	22 (35.5%)	21 (56.8%)	
RDI, events/h, median (IQR)	18.6 (10.4–31.1)	24.8 (10.4–41.7)	36.6 (20.0–54.7)	<.001
ODI, events/h, median (IQR)	7.3 (2.2–17.4)	9.8 (4.6–24.6)	24.5 (7.6–39.5)	<.001
No oxygen desaturation (ODI < 5)	355 (39.1%)	17 (27.4%)	7 (18.9%)	<.001
Mild oxygen desaturation (ODI 5 to < 15)	292 (32.2%)	22 (35.5%)	6 (16.2%)	
Moderate oxygen desaturation (ODI 15 to < 30)	135 (14.9%)	14 (22.6%)	9 (24.3%)	
Severe oxygen desaturation (ODI ≥ 30)	128 (13.9%)	9 (14.5%)	15 (40.5%)	
Sleep duration, h, median (IQR)	6.4 (5.4–7.2)	6.5 (5.3–7.2)	6.3 (5.2–7.3)	.854

(continued on following page)

Table 1—Demographic, clinical characteristics, and sleep study results. (*Continued*)

Characteristics	Number of Heart Failure Hospitalizations			*P*
	0 (n = 908)	1 (n = 62)	≥ 2 (n = 37)	
Duration SpO_2 < 90%, min, median (IQR)	0.5 (0.0–4.8)	1.4 (0.0–8.0)	12.4 (0.0–38.3)	.005
Percentage of sleep SpO_2 < 90%, %, median (IQR)	0.1 (0.0–1.4)	0.4 (0.0–2.6)	3.8 (0.0–10.0)	.003
Epworth Sleepiness Scale > 10, n (%)	5.0 (2.0–8.0)	6.0 (3.0–7.3)	4.0 (2.5–7.0)	.521
High-risk Berlin Questionnaire, n (%)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	.108

[a]Serum estimated glomerular filtration rate < 60 mL/min/1.73 m^2. AHI = apnea-hypopnea index, IQR = interquartile range, ODI = oxygen desaturation index, RDI = respiratory disturbance index, SpO_2 = arterial oxygen saturation.

presented with myocardial infarction (vs stable or unstable angina), lower left ventricular ejection fraction, larger atrial and ventricular dimensions, higher left ventricular mass, and higher pulmonary artery systolic pressure.

The characteristics of the CABG procedures are outlined in **Table 3**. There were no significant differences between the three groups with regard to the technical details of the CABG. Despite a significant difference in the length of stay between the three groups, the absolute difference in the median length of stay was less than 1 day. The medications prescribed upon hospital discharge are listed in **Table S1** in the supplemental material.

Cumulative incidence of heart failure hospitalizations

The cumulative crude incidences of heart failure hospitalizations over time, stratified by sleep apnea status, are shown in **Figure 2**. The event curves started to separate in the first 2 years, and the difference remained constant thereafter. The rate ratio for the cumulative incidence of heart failure hospitalizations between the sleep apnea and the nonsleep apnea group is shown in **Figure S1**. Within the first year, the rate ratio increased to more than 2.0 and appeared fairly constant thereafter.

Multivariate analyses of recurrent heart failure hospitalizations

The sleep apnea and nonsleep apnea groups incurred 127 and 52 heart failure hospitalizations over a total of 1,658.7 and 1,678.7 years of follow-up, respectively. Hence, the recurrent heart failure hospitalization rates were 0.077 (95% confidence interval [CI]: 0.023–0.039) person-years in the sleep apnea group and 0.031 (95% CI: 0.064–0.089) person-years in the nonsleep apnea group, giving an unadjusted rate ratio of 2.484.

Table 4 shows the hazard ratio for the conventional time-to-first-event analysis for heart failure hospitalization and the rate ratios for recurrent heart failure hospitalizations. The unadjusted rate ratio computed from the Poisson regression was 2.43 (95% CI: 1.76–3.36, $P < .001$). Similarly, the negative binomial regression gave an unadjusted rate ratio of 2.507 (95% CI: 1.77–3.56, $P < .001$). The Andersen–Gill model using robust standard errors gave an unadjusted hazard ratio of 2.48 (95% CI: 1.49–4.14, $P = .001$).

In addition to the sleep apnea group, the baseline covariates independently associated with heart failure hospitalizations were age, sex, hypertension, diabetes mellitus, left ventricular ejection fraction, ethnicity, family history of coronary artery disease, previous myocardial infarction, previous percutaneous coronary intervention, chronic kidney disease, and clinical presentation. In the partially adjusted model, sleep apnea was demonstrated to be independently associated with recurrent heart failure hospitalizations in the Poisson (1.74, $P = .002$), negative binomial (1.76, $P = .005$), and Andersen–Gill (1.80, $P = .031$) regressions. This association remained statistically significant after the Poisson (1.73, $P = .001$) and negative binomial (1.79, $P = .002$) regressions accounted for the competing risk of cardiovascular deaths.

The joint frailty model gave an estimate of the rate ratio for recurrent heart failure hospitalizations, which takes into account death as informative censoring, and an estimate of the hazard ratio for cardiovascular death, which accounts for the effect of hospitalizations on death. The estimated unadjusted rate ratio for heart failure hospitalizations was 2.32 (95% CI: 1.60–3.35, $P < .001$).

In the fully adjusted model, the rate ratio in the time-to-first-event analysis (1.72, $P = .021$) was higher than that in the Poisson regression (1.63, $P = .006$) and Andersen–Gill regression (1.66, $P = .047$) but lower than that in the negative binomial regression with cardiovascular deaths accounted for (1.83, $P = .003$). Despite a difference in rate ratios across statistical analyses, the absolute differences were minor and the rate ratios across all statistical analyses demonstrated a directionally similar trend.

DISCUSSION

In this analysis of patients who underwent a nonemergent CABG, at a mean follow-up of 3.3 years approximately 10% of the patients had at least one episode of heart failure hospitalization. Among those patients, a subgroup of 37% of patients had recurrent events that accounted for two-thirds of the total 179 heart failure hospitalization events. Using four robust statistical methods, we found that patients with sleep apnea had a 1.6- to 1.8-fold increased risk of recurrent heart failure hospitalization, even after adjustment for differences in baseline demographic and clinical characteristics.

Heart failure hospitalization is burdensome and costly. In 2014, there were approximately 1.1 million emergency department visits, 980,000 hospitalizations, and 84,000 deaths directly attributable to heart failure in the United States. The total estimated cost was over $11 billion. Due to the limited effectiveness of stents,[25,26] CABG is still widely performed. In patients discharged after a CABG, heart failure is the most common cause

Table 2—Diagnostic coronary angiography and echocardiography findings.

Characteristics	Number of Heart Failure Hospitalizations			*P*
	0 (n = 908)	1 (n = 62)	≥ 2 (n = 37)	
Coronary angiography				
Clinical presentation, n (%)				.013
ST-segment elevation myocardial infarction	98 (10.8)	6 (9.7)	5 (13.5)	
Non-ST-segment elevation myocardial infarction	338 (37.2)	28 (45.2)	24 (64.9)	
Unstable angina	180 (19.8)	14 (22.6)	3 (8.1)	
Stable angina	258 (28.4)	10 (16.1)	4 (10.8)	
Other	31 (3.4)	4 (6.5)	1 (2.7)	
No. of diseased coronary vessels, n (%)				.101
1	31 (3.4)	1 (1.6)	2 (5.4)	
2	119 (13.1)	5 (8.1)	0 (0.0)	
3	758 (83.5)	56 (90.3)	35 (94.6)	
Left main artery stenosis ≥ 50%	278 (30.6)	20 (32.3)	14 (37.8)	.643
Proximal left anterior descending artery stenosis ≥ 50%	672 (74.0)	49 (79.0)	26 (70.3)	.493
SYNTAX score, median (IQR)	33 (26.0–40.5)	36.5 (26.8–43.6)	34 (27.1–41.4)	.555
Echocardiography				
Left ventricular ejection fraction, median (IQR), %	55 (40–60)	45 (34–53)	35 (25–45)	<.001
Left atrium diameter, median (IQR), mm	39 (36–43)	41 (37–45)	42 (39–45)	.006
Left ventricular end-diastolic internal diameter, median (IQR), mm	50 (46–55)	54 (49–58)	60 (50–62)	<.001
Left ventricular end-systolic internal diameter, median (IQR), mm	34 (30–41)	41 (35–48)	49 (35–54)	<.001
Left ventricular mass index, median (IQR), g/m^2	101 (84–126)	115 (91–125)	128 (108–150)	.002
Aortic root diameter, median (IQR), mm	33 (30–35)	32 (29–35)	32 (29–35)	.222
E/A, median (IQR)	0.9 (0.7–1.2)	1.1 (0.6–1.5)	1.2 (0.8–2.3)	.052
Pulmonary artery systolic pressure, median (IQR), mm Hg	28.7 (24.4–35.0)	35.0 (29.2–49.0)	36.1 (25.5–54.0)	<.001

E/A = an echocardiographic marker of the diastolic function of the left ventricle, IQR = interquartile range, SYNTAX = synergy between percutaneous coronary intervention with Taxus and cardiac surgery.

of unscheduled hospitalization.[6] Thus, identifying patients at high risk has important implications for preventive efforts aimed at reducing the burden of post-CABG heart failure hospitalizations for both patients and society.

Our study showed that higher apnea-hypopnea index and higher oxygen desaturation index were associated with more heart failure hospitalizations after CABG (**Table 1**). The pathophysiological mechanisms by which sleep apnea leads to heart failure have been extensively reviewed.[27] Increased inspiratory efforts against the occluded pharynx generate exaggerated negative intrathoracic pressure, which increases the left ventricular transmural pressure. This in turn leads to increased venous return, causing distension of the right ventricle and leftward displacement of the interventricular septum during diastole. The impaired left ventricular filling reduces stroke volume. Additionally, oxygen desaturation during sleep impairs myocardial contractility by precipitating myocardial ischemia. There is also growing evidence that hypoxia exacerbates heart failure via a negative inotropic effect and sympathetic hyperactivity. To the best of our knowledge, this study is the first prospective cohort study to examine the relationship between sleep apnea and total heart failure hospitalizations in patients undergoing CABG.

Compared with the New Jersey cohort study, which showed that 19% of the patients had heart failure hospitalization at 2 years after CABG,[28] the risks were lower in our cohort (9.8% at 3.3 years after CABG) and in the Denmark National Registry study (8% at 1 year after CABG).[4] The most likely explanation is the different risk profile of the patients. Emergency CABG constituted 72.6% of the procedures in the New Jersey study but none of the procedures in our study and only 4% of those in the Danish study.

Statistical methods for total heart failure hospitalizations were initially applied to research into stable heart failure[16,29,30] and were recently extended to valve research.[17] Compared with prior studies on stable heart failure, where repeat events accounted for 46% of the total heart failure hospitalizations,[16,29] we found that in patients who underwent CABG repeat events accounted for 65% of the total heart failure hospitalizations. This suggests that repeat events are more frequent in post-CABG patients than in stable heart failure patients. Thus, it is relevant to use statistical methods to analyze repeat events in this cohort of patients.[13]

Screening of sleep apnea in patients scheduled for CABG and applying continuous positive airway pressure for those diagnosed with sleep apnea is not a standard practice at most Asian

Table 3—Coronary artery bypass grafting characteristics.

Characteristics	Number of Heart Failure Hospitalizations			*P*
	0 (n = 908)	1 (n = 62)	≥ 2 (n = 37)	
Operation type, n (%)				.479
Off-pump CABG	26 (2.9)	2 (3.2)	3 (8.1)	
On-pump CABG	880 (96.9)	59 (95.2)	34 (91.9)	
Hybrid CABG	2 (0.2)	0 (0.0)	0 (0.0)	
No. of bypass grafts, n (%)				.504
1–2	191 (21.0)	18 (29.0)	10 (27.0)	
3–4	705 (77.6)	43 (69.4)	27 (73.0)	
5–6	12 (1.3)	1 (1.6)	0 (0.0)	
No. of venous grafts, n (%)				.806
0–1	216 (23.8)	18 (29.0)	10 (27.0)	
2–3	682 (75.1)	43 (69.4)	27 (73.0)	
4–5	10 (1.1)	1 (1.6)	0 (0.0)	
LIMA graft, n (%)	866 (95.4)	58 (93.5)	34 (91.9)	.525
Non-LIMA arterial grafts, n (%)				.308
Radial artery or RIMA	57 (6.3)	2 (3.2)	0 (0.0)	
Radial artery and RIMA	12 (1.3)	0 (0.0)	0 (0.0)	
Concurrent valve operation, n (%)	62 (6.8)	4 (6.5)	3 (8.1)	.951
Total operation time, min, median (IQR)	288 (254.2–328.0)	277.5 (248.8–317.3)	300 (249–338.5)	.283
Estimated blood loss, mL, median (IQR)	200 (110–300)	200 (100–300)	300 (249–338.5)	.889
Length of stay, d, median (IQR)	9.0 (8.2–9.6)	9.5 (8.4–9.8)	9.2 (8.1–9.5)	.027

CABG = coronary artery bypass grafting, IQR = interquartile range, LIMA = left internal mammary artery, RIMA = right internal mammary artery.

institutions. Therefore, informing the patients about the sleep study findings within 1 month and offering a sleep clinic referral for those tested positive should be considered ethical and acceptable. The small number of the patients accepted continuous positive airway pressure could be related to low awareness.[31] Given the benefit in improving quality of life, more efforts are

Figure 2—Cumulative incidence of heart failure hospitalizations per 100 people, over time (in years), stratified by sleep apnea status.

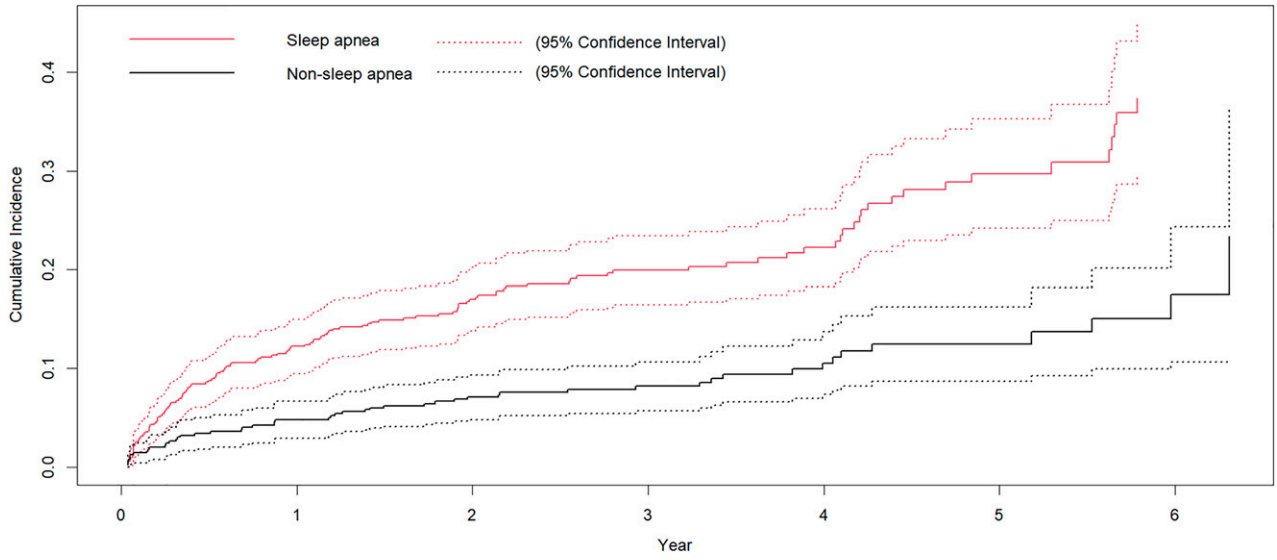

Table 4—Rate ratios for heart failure hospitalization.

Method	Model 1		Model 2		Model 3	
	Unadjusted RR (95% CI)	*P*	Adjusted RR[a] (95% CI)	*P*	Adjusted RR[b] (95% CI)	*P*
Cox regression	2.20 (1.44, 3.35)	<.001	1.69 (1.07, 2.66)	.025	1.72 (1.08, 2.72)	.021
Poisson regression with offset	2.43 (1.76, 3.36)	<.001	1.74 (1.23, 2.45)	.002	1.63 (1.15, 2.31)	.006
Negative binomial regression with offset	2.51 (1.77, 3.56)	<.001	1.76 (1.19, 2.63)	.005	1.71 (1.12, 2.62)	.013
Poisson regression with offset + cardiac death	2.36 (1.75, 3.16)	<.001	1.73 (1.26, 2.37)	.001	1.67 (1.21, 2.30)	.002
Negative binomial regression with offset + cardiac death	2.46 (1.78, 3.41)	<.001	1.79 (1.24, 2.59)	.002	1.83 (1.23, 2.72)	.003
Andersen and Gills (LWYY)	2.48 (1.49, 4.14)	.001	1.80 (1.05, 3.06)	.031	1.66 (1.01, 2.75)	.047
Joint frailty model	2.32 (1.60, 3.35)	<.001	1.73 (1.18, 2.63)	.006	1.72 (1.00, 3.01)	.056

Poisson and negative binomial regressions were estimated using the GENLIN function of IBM SPSS Statistics, LWYY regressions was estimated using the "reReg" package of R, and joint frailty models were estimated using the "frailtypack" package of R. [a]Model 2: Competing risk regression adjusted for age, sex, hypertension, diabetes, and left ventricular ejection fraction. [b]Model 3: Competing risk regression adjusted for age, sex, hypertension, diabetes, left ventricular ejection fraction + ethnicity, family history of coronary artery disease, previous myocardial infarction, previous percutaneous coronary intervention, chronic kidney disease, and clinical presentation. CI = confidence interval, LWYY = Lin–Wei–Yang–Ying semiparametric regression approach, RR = rate ratio.

needed to increase the adoption of obstructive sleep apnea therapy. Regardless, our study suggests that a simple sleep study may be able to identify patients who are prone to recurrent heart failure hospitalization after CABG. Future research should focus on the potential role of continuous positive airway pressure and adjunctive therapies such as cardiac rehabilitation and weight reduction in reducing post-CABG heart failure hospitalization in patients with sleep apnea.

We found that 51% of the patients have sleep apnea. This prevalence, although high, is consistent with other published studies on patients with coronary artery disease undergoing CABG.[7,8] Besides, it has been shown that the restrictive craniofacial phenotype of the East Asians increases the susceptibility to upper airway obstruction.[32]

Our study should be interpreted in due consideration of the limitations. First, this is an ancillary study of the SABOT study and was not included in the power calculations for the original study protocol. Therefore, our findings should be considered exploratory rather than confirmatory. Second, quality-of-life measures related to the recurrent heart failure hospitalizations were not captured. Third, although we captured data for medication on discharge, data on postdischarge optimization of and adherence to medication, especially in patients who had heart failure hospitalizations, were not available. Fourth, the Watch-PAT 200 used in this study was unable to differentiate obstructive from central events. Hence, we could not be certain regarding the underlying pathophysiology of the heart failure hospitalizations. Last, all patients in the SABOT trial underwent nonemergent CABG, and we are uncertain whether the same findings would be observed in patients undergoing emergent CABG.

CONCLUSIONS

In patients undergoing nonemergent CABG we demonstrated that sleep apnea was independently associated with higher recurrent hospitalizations for heart failure. Our data compellingly spotlight the importance of future research into therapeutic approaches aimed at mitigating sleep apnea in patients undergoing CABG so as to minimize long-term heart failure complications.

ABBREVIATIONS

CABG, coronary artery bypass grafting
CI, confidence interval
SABOT, Sleep Apnea and Bypass Operation

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